

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-283/S011

Administrative/Correspondence

Time Sensitive Patent Information
Pursuant to 21 C.F.R. 314.53
for
NDA 21-283

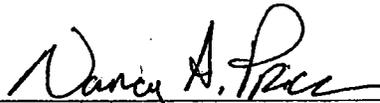
The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

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

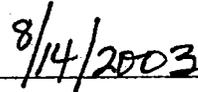
U.S. Patent Number: U.S. 5,399,578
Expiration Date: March 21, 2012
Type of Patent: Drug Substance, Drug Product and Method of Use
Name of Patent Owner: Novartis Pharmaceuticals Corporation

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 heart failure in ACEI intolerant patients and is the subject of this application for the treatment of post myocardial infarction, for which approval is being sought.

Signed



Date



Nancy A. Price
Director
Drug Regulatory Affairs

EXCLUSIVITY SUMMARY

NDA # 21-283

SUPPL # 011

HFD # 110

Trade Name Diovan

Generic Name valsartan Tablets

Applicant Name Novartis

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1) 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 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.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

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?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES NO

IF THE ANSWER TO QUESTION 2 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 NO

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

NDA#

NDA#

NDA#

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

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. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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:

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"):

VALIANT Trial (VAL489E)

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 # 40,783 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?

Investigation #1
YES ! NO

Explain:

! Explain:
Not Applicable

Investigation #2

!

!

YES

! NO

Explain:

! 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

If yes, explain:

Name of person completing form: Edward Fromm
Title: Supervisory Consumer Safety Officer
Date: 4/27/05

Name of Office/Division Director signing form:
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Norman Stockbridge
4/29/05 06:49:19 AM

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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-283 Supplement Type (e.g. SE5): SE1 Supplement Number: 011

Stamp Date: December 17, 2003 Action Date: October 17, 2004

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

Applicant: Novartis Pharmaceuticals Therapeutic Class: 6S

Indication(s) previously approved:

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

Number of indications for this application(s): 1

Indication #1: treatment of patients with post-myocardial infarction (MI)

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 _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ 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): _____

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}

Edward Fromm
Regulatory Project Manager

cc: NDA 21-283
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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/s/

Edward Fromm
9/2/04 11:51:29 AM

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JUL 22 1998

Minutes
July 14, 1998
IND 40,783 Valsartan
Novartis Pharmaceuticals Corporation
End-of-Phase 2 Meeting, Part 2:
Valsartan Post-Myocardial Infarction

Related submission: June 26, 1998; serial number 055

Date of Request for Meeting: May 28, 1998

Attending:

Novartis:

Malcolm MacNab, M.D., Ph.D.	Vice President, Clinical Research
Marc Henis, M.D.	Clinical Research
Susan Edwards	Clinical Research
Eric Neuhart, M.D.	Clinical Research, Basle, Switzerland
Tom Chiang, Ph.D.	Associate Director, Biostatistics
Jim Pensabene	Executive Director, Diovan Project Team Leader
Adrian Birch	Executive Director, Drug Regulatory Affairs
Nancy Price	Associate Director, Drug Regulatory Affairs
Marc Pfeffer, M.D.	Primary Investigator, VALIANT trial; Harvard Medical School

FDA:

Robert Temple, M.D.	HFD-101	Office Director/Chair
Rachel Behrman, M.D.	HFD-101	Deputy Office Director
Raymond Lipicky, M.D.	HFD-110	Division Director
Charles Ganley, M.D.	HFD-110	Group Leader/Medical & Medical Officer
James Hung, Ph.D.	HFD-710	Statistician
Kathleen Bongiovanni	HFD-110	Regulatory Health Project Manager/ Minutes Recorder

Background: Novartis requested this meeting as a follow-up to the May 8, 1998 meeting, to continue the discussion of their planned phase 3 protocol to investigate the use of valsartan post-myocardial infarction, alone or with captopril, to improve survival and decrease the risks of failure-related hospitalization and progression to severe/resistant heart failure. This trial will be called VALIANT, Valsartan in Acute Myocardial Infarction.

Conclusions from May 8, 1998 Meeting:

- Novartis will submit a full explanation of the rationale for their choice of completed trials to serve as a basis for their calculations of an appropriate margin in a non-inferiority trial, and they will also submit external validation from those trials.
- Novartis will consider the questions raised about the design of the superiority trial.
- The proposed adverse event reporting plan is acceptable.
- Novartis will come back for additional discussion about these issues.

Issues:

Choice of completed trials with high-risk patients: SAVE, AIRE, and TRACE
Criteria for non-inferiority of valsartan over captopril and the magnitude of the margin

Meeting:

Choice of Margin:

The group agreed that the major remaining issue that needs to be addressed is the size of the non-inferiority margin, the difference between new and control treatments, that, if exceeded (as indicated by an upper bound of the 95% confidence interval for that difference) would mean that the new drug had not been shown to have an effect. The margin chosen should be the smallest effect the control group can reliably be presumed to have (compared to an untreated group) in the study. The larger the margin, the easier it is to show non-inferiority to it.

Dr. Temple explained that the use of an active control non-inferiority trial in most settings, including this one, is fraught with problems, and at this time there is no well-established method for choosing the margin. Novartis proposed basing their calculation of the effect of the control (captopril) on the pooled results of the SAVE, AIRE, and TRACE trials, using the mean value in the trials. It would be more difficult for the firm if they based their calculations on SAVE alone, because the drug effect in the SAVE study was smaller than in the other trials.

Dr. Temple thought the identified margin was too large, not "conservative." He said that the margin could be based on the lower bound of the 95% confidence interval of the difference between control and placebo of the pooled results, about 17%, rather than the firm's proposed use of 26%. The margin they had proposed was larger than the effect of captopril in the SAVE study and we did not (and could not) know that all three drugs had the same effect. Use of the 95% lower bound, however, was conservative enough. In addition, because the new agent should preserve at least half of the control effect, the non-inferiority margin should be 50% x 17, or about 9%. but this should not be taken as absolute. Dr. Lipicky noted that if the firm does the trial, and the 95% confidence interval for the drug-control difference is slightly greater than 9%, they could still submit the supplement, but they would not have our up-front assurance that it would be adequate.

Dr. Temple encouraged the firm to keep abreast of developments in establishing methods for choosing margins, including Advisory Committee meetings, journal articles, and other Agency decisions.

Superiority Trial:

Dr. Temple told the firm that if valsartan beats the active control, they would be given credit for having beaten an active drug rather than placebo; a very powerful finding.

Choice of Patients:

Dr. Temple noted that the patients that Novartis is proposing to include in the VALIANT trial are somewhat more symptomatic than the patients in SAVE, AIRE, and TRACE, and that may lead to a greater effect. We believe that is acceptable.

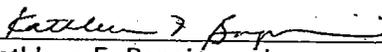
Contents of Submission:

We recommended that Novartis include in any supplement their rationale for the choice of the trials used for the external validation of the ACE inhibitor/placebo effect, for the margin they choose, and for the choice of captopril as the active control.

P-Value Adjustment:

Dr. Hung said that he has some recommendations on the p-value adjustment for the non-inferiority test. He will discuss them in detail with the firm at a later time.

Signature, minutes preparer:


Kathleen F. Bongiovanni

7-22-98

Concurrence Chair:


Robert Temple, M.D.

7/22/98

Minutes of a Meeting between Novartis and the FDA

Date: September 16, 2003

Application: IND 40,783
Diovan (valsartan)

Indication: Valsartan use post-myocardial infarction, alone or with Captopril, to improve survival and decrease the risks of failure-related hospitalization and progression to severe/resistant heart failure (VALIANT trial-Valsartan in Acute Myocardial Infarction).

Applicant: Novartis Pharmaceuticals Corporation

Subject: Discussion of VALIANT Study Results

FDA participants

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research I
Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D., HFD-110, Deputy Division Director
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Mehul Desai, M.D., HFD-110, Medical Officer
Salma Lemtouni, M.D., HFD-110, Medical Officer
Katharine Lillie, M.D., HFD-110, Medical Officer
Edward Fromm, HFD-110, Regulatory Health Project Manager

Novartis

Marc Pfeffer, M.D., VALIANT Study Chairman, Harvard Medical School
Malcolm MacNab, M.D., Ph.D., Vice President, Cardiovascular Clinical Development & Medical Affairs (CD&MA)
Francis Plat, M.D., Executive Director, Cardiovascular CD&MA
Steven Zelenkofske, M.D., Director, Cardiovascular CD&MA
Susan Edwards, Associate Director, Cardiovascular CD&MA
Tom Chiang, Ph.D., Director, Biostatistics and Statistical Reporting
Jim Gong, Ph.D., Associate Director, Biostatistics and Statistical Reporting
Pratapa Prasad, Ph.D., Director, Clinical Pharmacology
Mr. Adrian Birch, Executive Director, Drug Regulatory Affairs
Ms. Nancy Price, Director, Drug Regulatory Affairs

Background

Novartis requested this meeting to discuss the results of the VALIANT trial, which tested whether valsartan, would be more effective than, or at least as effective as, captopril, and whether the combination of captopril and valsartan would be more effective than captopril alone in the reduction of all-cause mortality in high risk patients with an acute MI. After discussions with the Agency in 1998, the study began and enrolled approximately 14,500 patients before ending this year.

Novartis plans to present the results of the VALIANT study on November 10, 2003, at the American Heart Association meeting and will formally submit the results of the study as a supplement in December 2003.

Meeting

Novartis opened the meeting by presenting a slide that outlined the three major objectives of the study for the primary endpoint of reduction of all cause mortality after MI:

- Valsartan is more effective than captopril alone
- Valsartan plus captopril is more effective than captopril alone
- If valsartan is not shown more effective than captopril, to demonstrate that valsartan is not inferior to captopril.

To validate the control group (captopril) with respect to the non-inferiority analysis with valsartan, the sponsor chose three placebo-controlled mortality trials (SAVE, AIRE, TRACE) that had high-risk patients with MI. The SAVE trial, in particular, compared captopril at 50 mg three times/day versus placebo. Captopril was rapidly up-titrated to this dose in the SAVE trial and the same approach was taken with regards to the VALIANT trial.

After discussions with the Agency in 1998, the non-inferiority margin the sponsor set the margin at 13% and prespecified it in the protocol. A hazard ratio of 1.13 was defined as the threshold for the non-inferiority assessment between valsartan and captopril. The details of how that 13%, representing a 50% retention of the documented effect of the control drug class, were not discussed, but the Agency accepted the calculation in 1998.

Novartis explained that the primary endpoint in the trial was the time to all cause mortality and some of the secondary endpoints included time to first event of cardiovascular mortality and a combination of cardiovascular mortality, reinfarction, and hospitalization for heart failure. The confidence limits for the primary comparisons (valsartan alone or the combination versus captopril alone) were chosen to preserve 50% of the nominal effect of captopril alone, with each comparison allocated two-sided alpha of 0.0253. Covariates in the study were age of the patient and primary patient history of MI. The endpoints chosen for the VALIANT trial were based on those in the ACE inhibitor trials (e.g., SAVE, AIRE) and also on the recommendation of the Adjudication Committee for the study.

Novartis noted that the primary analysis population of the study will include all randomized patients and that the per-protocol population will consist of those patients that received at least one dose of study drug and met the entry the MI entry criteria. They added that there was close to an even distribution between the two groups in the per-protocol population. Dr. Temple suggested that a better analysis would result if the sponsor would separate the per-protocol analyses into those patients who satisfied the MI criteria and those patients who received at least one dose of study medication.

Interim Analyses

Dr. Throckmorton asked for clarification about the 7 interim analyses that were conducted for this study. The sponsor replied that 2 of the interim analyses were for efficacy (i.e., superiority and all-cause mortality) while the remaining interim analyses were solely for safety.

Results of the Study

Novartis said that the primary endpoint analysis with regard to all-cause mortality showed that valsartan was not more effective than captopril. In addition, a combination of valsartan and captopril was not more effective than captopril alone. However, they believe that the study showed that valsartan was not inferior to captopril and could be used as an alternative to captopril.

Novartis noted that subgroup analyses were consistent with the primary analysis results. There also appeared to be no interaction between beta blockers and the combination of valsartan and captopril. Dr. Temple suggested

that when these data are submitted as a supplement, the sponsor should detail this lack of an interaction and the fact that previous ACE inhibitor trials have had about a 30% beta blocker use.

Dr. Karkowsky asked if patients could have an ICD while participating in the trial. The sponsor replied that patients could have an ICD while in the trial.

Dr. Stockbridge asked what percentage of patients received open-label ACE inhibitor and what doses were used. Novartis replied that about 10-11% of patients received open-label ACE inhibitor during the open-label phase but were unable to say what doses were used in this phase of the study. Dr. Stockbridge asked how the study results would be affected if the ACE inhibitor use in the open-label phase were censored. The sponsor replied that the results would likely be the same.

Safety

The sponsor pointed out that the prespecified adverse events of symptomatic hypotension, renal dysfunction, dry cough, and angioedema were consistent for the three groups (valsartan, valsartan + captopril, captopril) to what was expected prior to initiation of the trial. Dr. Throckmorton asked what was the most severe angioedema reported. Novartis replied that the cases reported were mild in nature and that no deaths or intubations occurred.

Other Questions

1. Does FDA agree that the results from VALIANT provide a sufficient basis for obtaining an indication in post-myocardial infarction patients?

This will need to be determined during review. The 13% non-inferiority margin chosen seemed high on its face, but the Agency had accepted it in 1998. The sponsor should provide full details of the derivation of the non-inferiority margin.

2. Based on the information presented, could FDA offer a preliminary opinion regarding the review designation (priority or standard)? Does the Agency anticipate Advisory consultation with the Cardio-Renal Advisory Committee?

Dr. Throckmorton said he said that his preliminary opinion on the review designation (priority or standard) was that it would be a standard (10 month review). He said this therapy does not appear to offer any clear advantages over available therapy for this disease state. Of course, the data will have to be submitted before a more thorough and final determination could be made.

Dr. Throckmorton said that he could not say, at the present time, whether the study would be presented before the Cardio-Renal Advisory Committee. The sponsor asked if the dates of the Advisory Committee Meeting were known for the next year. Dr. Throckmorton said he was not sure of the future meeting dates of the Advisory Committee but suggested the sponsor contact Mr. Fromm after the meeting to see if those dates were known.

3. Does FDA agree that it is acceptable to omit the Summary of Clinical Efficacy (CTD Section 2.7.3) and the Summary of Clinical Safety (Section 2.7.4)?

Dr. Throckmorton said it was acceptable.

**APPEARS THIS WAY
ON ORIGINAL**

Minutes Preparation:

Edward Fromm

Concurrence, Chair:

Robert Temple, M.D.

drafted/ef: 10/02/03-10/08/03-10/14/03

Rd: DThrockmorton-10/8/03
NStockbridge-10/8/03
AKarkowsky-10/7/03
MDesai-10/6/03
SLemtouni-10/6/03
KLillie-10/6/03
DCT 10.8.03

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/s/

Edward Fromm

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Dr. Temple signed the minutes on October 15, 2003.

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Integrated Summary of Efficacy

Per the meeting with Novartis on September 16, 2003, Dr. Throckmorton stated that it was permissible to omit the Summary of Clinical Efficacy (CTD Section 2.7.3).

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Integrated Summary of Safety

Per the meeting with Novartis on September 16, 2003, Dr. Throckmorton stated that it was permissible to omit the Summary of Clinical Safety (CTD Section 2.7.3).

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Memorandum DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS

DATE: 3/09/04

FROM: Anthony G. Proakis, Ph.D., Pharmacology/Toxicology Reviewer, HFD-110

TO: Files

SUBJECT: NDA # 21,283/S-011

Novartis submitted this efficacy supplement for Diovan[®] Tablets for reduction in cardiovascular and total mortality following myocardial infarction on 12/17/03. This proposed indication for Diovan[®] Tablets is based on results of a clinical study (VALIANT, Valsartan in Acute Myocardial Infarction Trial) in post-myocardial infarction patients.

This supplemental application contains no new non-clinical pharmacology/toxicology study reports requiring review.

Likewise, the sponsor's proposed changes to the current product labeling are limited to the clinical information section and they propose no changes from the previously approved summaries of the non-clinical studies. Therefore, a pharmacology/toxicology review for this NDA supplement is not necessary.

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/s/

Anthony Proakis
3/9/04 02:07:32 PM
PHARMACOLOGIST

Charles Resnick
3/9/04 03:27:44 PM
PHARMACOLOGIST

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NDA 21-283

Financial Disclosure by Clinical Investigators

Author(s): Jeanne Kaczor
Document type: Section 19 of NDA
Document status: Final
Release date: 04-Dec-03
Number of pages: 4

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Attachments:

FDA Form 3454

FDA Form 3455

Signed Novartis Forms of Investigators with something to disclose

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1 Financial Disclosure (FD) FDA Forms

- FDA Form 3454: Included with attached list of principal investigators
- FDA Form 3455: Included with attached forms detailing information which needs to be disclosed

2 Process used to collect information

The following process was used to collect information:

- Letters were sent out to principal investigators for the appropriate study requesting financial disclosure information. A synopsis of the Financial Disclosure Regulation and certification/disclosure forms was included with the letter. Principal investigators were instructed to provide information for themselves.
- If no reply was received to the initial letter, a follow-up letter was sent to principal investigators.
- A signed financial disclosure form received from an investigator with none of the information boxes checked has been interpreted by Novartis to indicate that the investigator had no financial information to disclose.
- At study close out or as part of a retrospective collection of information, the principal investigators were instructed to update Novartis for one year from last patient last visit, if the status of their financial disclosure status changed.
- Retrospective collection of financial disclosure information was applied for studies on going on 2/2/99.

3 Description of Spreadsheets

The spreadsheets provided with this document detail all the principal investigators participating in studies conducted at US & non-US sites. The information is presented in columns by center number, principal investigator, study facility and address. For all investigators with information to disclose, the details are provided in individual forms that are placed behind FDA Form 3455 and included with this document.

4 Summary of Findings

No principal investigators were full or part-time employees of Novartis Pharmaceuticals Corporation. Financial arrangements and interests which require disclosure are identified on the spreadsheets next to the investigator's name and are detailed in the disclosure forms that follow FDA Form 3455. These arrangements and interests were as follows:

Investigator	Study No.	Center No.	Amount Disclosed	Category of Disclosure
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____

Any bias resulting from these arrangements is minimized by independent data monitoring by Novartis; multiple investigators used in the study and a double-blind, active controlled trial design.

Retrospective collection of financial disclosure information was applied for study 0108 because it was ongoing on 2/2/99.

Percent of Investigators who responded:

- Study No. 0108
 - US Centers: 100% of investigators responded (443 of 443 PIs)
 - Non-US Centers: 99% of investigators responded (636 of 637 PIs)

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CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached spreadsheet.	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Francis Plat, M.D.	TITLE Diovan Clinical Project Leader
FIRM / ORGANIZATION Novartis Pharmaceuticals Corporation	
SIGNATURE 	DATE Nov 27. 03

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Name of clinical investigator
Name of clinical study

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Francis Plat, M.D.	TITLE Diovan Clinical Project Leader
FIRM / ORGANIZATION Novartis Pharmaceuticals Corporation	
SIGNATURE 	DATE Nov 27. 03

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

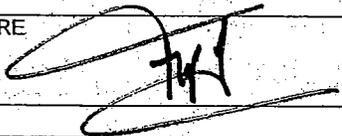
The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

name of clinical investigator
Name of clinical study

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Francis Plat, M.D.	TITLE Diovan Clinical Project Leader
FIRM / ORGANIZATION Novartis Pharmaceuticals Corporation	
SIGNATURE 	DATE Nov 27.03

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

Novartis
CERTIFICATION/DISCLOSURE FORM
 Financial Disclosure by Clinical Investigators

1. Study Name: VALIANT (VALsartan In Acute myocardial Infarction) Multicenter, multinational, double-blind randomized, active controlled, parallel group study comparing the efficacy and safety of long-term treatment with valsartan, captopril and their combination in high-risk patients after myocardial infarction.	
2a. Protocol number: _____	2b. Site Number: _____
3. Investigator <input type="checkbox"/> _____	
4. Investigator/subinvestigator Name: _____	
5. Address: _____	
6. Telephone: _____	f. Fax: _____
8. Indicate by marking Yes or No if any of the financial interests or arrangements with Novartis of concern to FDA apply to you, your spouse, or dependent children and describe the financial interests or arrangements below.	
Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Financial Arrangements whereby the value of the compensation could be influenced by the outcome of the study. This could include, for example, compensation that is explicitly greater for a favorable outcome, or compensation to the investigator in the form of an equity interest in the sponsor or in the form of compensation tied to sales of the product such as a royalty interest. If yes, please describe: _____ _____ _____
Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Significant payments of other sorts, excluding the costs of conducting the study or other clinical studies. This could include, for example, payments received by the investigator to support activities that have a monetary value greater than \$25,000 (i.e. a grant to the investigator or the institution to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria). If yes, please describe: _____ _____ _____
Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	A proprietary or financial interest in the test product such as a patent, trademark, copyright, or licensing agreements. If yes, please describe: _____ _____ _____
Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	A significant equity interest in the sponsor of the study. This would include, for example, any ownership interest stock options, or other financial interest whose value cannot be easily determined through reference to public prices, or any equity interest in a publicly traded company exceeding \$50,000. If yes, please describe: _____ _____ _____
or <input type="checkbox"/> I hereby certify that none of the financial interest or arrangements listed above exist for myself, my spouse, or my dependent children. In accordance with 21 CFR Parts 54.1 to 54.8, I declare that the information provided on this form is, to the best of my knowledge and belief, true, correct, and complete. Furthermore, if my financial interests and arrangements, or those of my spouse and dependent children, change from the information provided above during the course of the study or within one year after the last patient has completed the study as specified in the protocol, I will notify the VALIANT coordinating center promptly.	
9. Name: (please print) _____	10. Date _____
Signature: _____	

Novartis
CERTIFICATION/DISCLOSURE FORM
Financial Disclosure by Clinical Investigators

1. Study Name: <u>VARIANT (Valsartan in Acute Myocardial Infarction) Multicenter, nonblinded, double-blind randomized, active controlled, parallel group study comparing the efficacy and safety of long-term treatment with valsartan, captopril and their combination in high-risk patients after myocardial infarction</u>	
2. Protocol number: _____	2b. Site Number: _____
3. Investigator: _____	Subinvestigator: _____
4. Investigator/subinvestigator name: _____	
5. Address: _____	
6. Telephone: _____	7. Fax: _____
8. Indicate by marking yes or No if any of the financial interests or arrangements with Novartis of concern to FDA apply to you, your spouse, or dependent children and describe the financial interests or arrangements below.	
Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Financial Arrangements whereby the value of the compensation could be influenced by the outcome of the study. This could include, for example, compensation that is explicitly greater for a favorable outcome, or compensation to the investigator in the form of an equity interest in the sponsor or in the form of compensation tied to sales of the product such as a royalty interest. If yes, please describe: _____ _____
Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	Significant payments of other sorts, received during the course of the trial or for one year following completion of the trial, excluding the costs of conducting the study or other clinical studies. This could include, for example, payments received by the investigator to support activities that have a monetary value greater than \$25,000 (i.e. a grant to the investigator or the institution to fund ongoing research, compensation in the form of equipment). If yes, please describe: _____ _____
Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	A proprietary or financial interest in a test product such as a patent, trademark, copyright, or licensing agreements. If yes, please describe: _____ _____
Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	A significant equity interest in the sponsor of the study during the course of the trial and for one year following completion of the trial. This would include, for example, any ownership interest stock options, or other financial interest whose value cannot be easily determined through reference to public prices, or any equity interest in a publicly traded company exceeding \$50,000. If yes, please describe: _____ _____
or	
<input type="checkbox"/> I hereby certify that none of the financial interest or arrangements listed above exist for myself, my spouse, or my dependent children.	
In accordance with 21 CFR Parts 54.1 to 54.8, I declare that the information provided on this form is, to the best of my knowledge and belief, true, correct, and complete. Furthermore, if my financial interests and arrangements, or those of my spouse and dependent children, change from the information provided above during the course of the study or within one year after the last patient has completed the study as specified in the protocol, I will notify Novartis promptly.	
9. Name: (please print) _____	10. Date _____
Signature: _____	_____

Novartis
CERTIFICATION/DISCLOSURE FORM
Financial Disclosure by Clinical Investigators

1. Study Name: VALIANT (VALsartan In Acute myocardial INfarction) Multicenter, multinational, double-blind randomized, active controlled, parallel group study comparing the efficacy and safety of long-term treatment with valsartan, captopril and their combination in high-risk patients after myocardial infarction.	
2. Protocol numbers: _____	2b. Site Number: _____
3. Investigator <input type="checkbox"/>	Subinvestigator <input checked="" type="checkbox"/>
4. Investigator/subinvestigator Name: _____	
5. Address: _____	
6. Telephone: _____	7. Fax: _____
8. Indicate by marking Yes or No if any of the financial interests or arrangements with Novartis of concern to FDA apply to you, your spouse, or dependent children and describe the financial interests or arrangements below:	
Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Financial Arrangements whereby the value of the compensation could be influenced by the outcome of the study. This could include, for example, compensation that is explicitly greater for a favorable outcome, or compensation to the investigator in the form of an equity interest in the sponsor or in the form of compensation tied to sales of the product such as a royalty interest. If yes, please describe: _____ _____
Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Significant payments of other sorts, received during the course of the trial or for one year following completion of the trial, excluding the costs of conducting the study or other clinical studies. This could include, for example, payments received by the investigator to support activities that have a monetary value greater than \$25,000 (i.e. a grant to the investigator or the institution to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria). If yes, please describe: _____ _____
Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	A proprietary or financial interest in the test product such as a patent, trademark, copyright, or licensing agreements. If yes, please describe: _____ _____
Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	A significant equity interest in the sponsor of the study during the course of the trial and for one year following completion of the trial. This would include, for example, any ownership interest stock options, or other financial interest whose value cannot be easily determined through reference to public prices, or any equity interest in a publicly traded company exceeding \$50,000. If yes, please describe: _____ _____
or	
<input type="checkbox"/> I hereby certify that none of the financial interest or arrangements listed above exist for myself, my spouse, or my dependent children.	
In accordance with 21 CFR Parts 54.1 to 54.8, I declare that the information provided on this form is, to the best of my knowledge and belief, true, correct, and complete. Furthermore, if my financial interests and arrangements, or those of my spouse and dependent children, change from the information provided above during the course of the study or within one year after the last patient has completed the study as specified in the protocol, I will notify Novartis promptly.	
9. Name: (please _____)	10. Date _____
Signature: _____	_____

Statement of financial support received as co-principal investigator of the VALIANT trial

Compensation arrangement: Novartis paid a fraction of my salary (varying between 10 and 20% depending on the phase of the study) for the duration of VALIANT. My income derives from my _____ salary and from private earnings. Novartis paid 10-20% of both parts of my income – the appropriate part to _____ and the other part to me directly. Approximately half of a secretarial salary was also paid to _____ along with some office expenses. All _____ payments attracted overheads. The amounts paid are as follows:

_____ Start Date 1/1/1999 - End Date 12/31/2003

_____ Start Date 12/1/1999 - End Date 12/31/2003

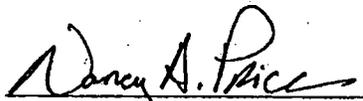
	Contracted Amt	Paid To Date	Contracted Amt
_____	_____	_____	_____
_____	_____	_____	_____

NDA No. 21-283

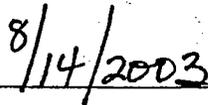
Diovan®
(valsartan) Tablets
New Drug Application

**NOVARTIS CERTIFICATION
IN COMPLIANCE WITH THE
GENERIC DRUG ENFORCEMENT ACT OF 1992**

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



Nancy A. Price
Director
Drug Regulatory Affairs



Date



1-13-04

NDA 21-283/S-011

PRIOR APPROVAL SUPPLEMENT

Novartis Pharmaceuticals Corporation
Attention: Ms. Nancy A. Price
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Price:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Diovan® (valsartan) 40, 80, 160, and 320 mg Tablets

NDA Number: 21-283

Supplement number: 011

Review Priority Classification: Standard (S)

Date of supplement: December 17, 2003

Date of receipt: December 17, 2003

This supplemental application proposes the use of Diovan® (valsartan) for the treatment of patients post-myocardial infarction (MI).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 15, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 17, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application, and we are waiving the pediatric study requirement for this application.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call:

Mr. Edward Fromm
Regulatory Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Doug Throckmorton
1/13/04 04:03:51 PM

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**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

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Transmitted to FAX Number: (973) 781-3590

Attention: Ms. Nancy Price

Company Name: Novartis Pharmaceuticals

Phone: (862) 778-3591

Subject: Confirmation of Telecon w/FDA
NDA 21-283/S-011
Diovan (valsartan) Tablets

Date: September 3, 2004

Pages including this sheet: 2

From: Edward Fromm
Phone: 301-594-5332
Fax: 301-594-5494

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

Confirmation of Telecon

Drug: NDA 21-283/S-011, Diovan (valsartan) Tablets

Sponsor: Novartis Pharmaceuticals

Subject: VALLANT Review

Date Requested: September 2, 2004

Date Confirmation Faxed: September 3, 2004

Telecon Date: September 9, 2004

Telecon Time: 10:30A.M. to 11:00 A.M.

FDA Participants:

Norman Stockbridge, M.D., Ph.D., HFD-110, Acting Division Director, Division of Cardio-Renal Drug Products
Edward Fromm, HFD-110, Acting Chief, Project Management Staff

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On Original*

Minutes of a Telephone Conference Call between Novartis and the FDA

Date: September 9, 2004

Application: NDA 21-283/S-011
Diovan (valsartan) Tablets

Sponsor: Novartis Pharmaceuticals, Inc.

Subject: Discussion of Review of VALIANT Study

FDA Participants

Norman Stockbridge, M.D., Ph.D., HFD-110, Acting Director, Division of Cardio-Renal Drug Products
Edward Fromm, HFD-110, Chief, Project Management Staff

Novartis

Francis Plat, M.D. – Executive Director, Cardiovascular CD&MA
Angelo Trapani – Clinical Research Manager, Cardiovascular CD&MA
Tom Chiang, Ph.D. – Director, Biostatistics and Statistical Reporting
Jim Gong, Ph.D. – Associate Director, Biostatistics and Statistical Reporting
Math Hukkelhoven, Ph.D. - Global Head, Drug Regulatory Affairs
Adrian Birch – Executive Director, Drug Regulatory Affairs
Nancy Price – Director, Drug Regulatory Affairs

Background

This efficacy supplement, submitted on December 17, 2003, contains the results of the VALIANT (VALsartan In Acute myocardial infarction) trial, a randomized, controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and signs, symptoms or radiologic evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction. Novartis believes that valsartan in the overall VALIANT study population, demonstrated equivalent efficacy to captopril. They also believe that valsartan was shown to be efficacious and safe in post-myocardial infarction patients who did not receive ACE inhibitor therapy.

Clinical investigations of Diovan for the treatment of post myocardial infarction in the United States were conducted under IND 40,783. The telecon today is to discuss the progress of the review to date of this supplement.

Telecon

Dr. Stockbridge began the telecon by noting that the review of the VALIANT supplement to date has not found enough evidence to support approval. He added that Dr. Temple has been briefed on the application and concurs with the view that approval is not likely given the current database for the supplement.

Dr. Stockbridge outlined the following issues that need resolved before approval could be granted:

- The historical basis for the effect of captopril was the SAVE trial, which used captopril alone, along with a combination of the AIRE and TRACE trials, which did not use captopril and had larger treatment effects. An analysis of the VALIANT data based on SAVE alone for historical context does not show compelling evidence for preservation of even 50% or the effects of captopril, so there is no way to establish “non-inferiority” of valsartan with captopril, especially given the endpoints of mortality or hospitalization.
- Historical constancy-Is the treatment effect of SAVE relevant to the background therapy in the VALIANT trial? Dr. Stockbridge noted that the use of beta-blockers in SAVE was low (<20%), yet around 80% in VALIANT. This is a concern for the Division because there is expectation (at least partly from Val-HeFT)

that use of beta-blockers and ACE inhibitors have no additive effect and in fact may be adverse to one another.

Other, more minor issues

- Discontinuation rates among the treatment groups were not equal
- Open-label use of ACE Inhibitors and angiotensin receptor antagonists
- Compliance may have not equal between the treatment groups, given that valsartan was given twice-daily while captopril was given three times daily.

Novartis said they believe that a historical basis of effect of captopril could be based on SAVE alone. Dr. Stockbridge replied that of the 3 trials (SAVE, AIRE, and TRACE), SAVE shows the least effect, inflates the treatment effect with respect to the comparator, and reduces variance for this estimate.

Novartis noted that at a 1998 meeting with the Agency regarding the VALIANT trial, the Agency accepted the 13% non-inferiority margin proposed by the sponsor. Dr. Stockbridge said he did not reach this conclusion when reviewing the minutes of the 1998 meeting, but nevertheless said it has not been the policy of the Agency to "raise the bar" after agreement has been reached on important issues. He noted, however, our biggest concern with the application was the use of beta-blockers in the trial, a use that could offset any effect of captopril and make a comparison with valsartan meaningless.

Novartis asked how they could address these issues so that a not approvable letter did not issue. Dr. Stockbridge stated that some options are as follows:

- Obtain additional information about background therapy in the trial
- Make an argument that the use of beta-blockers did not interfere with the effect of captopril
- Find additional data on the use of beta-blockers in the AIRE and TRACE studies.

Novartis asked if it would be helpful to do a subgroup analysis of the VALIANT study based on whether patients received a beta-blocker or did not receive one. Dr. Stockbridge said this data could be helpful. He encouraged the sponsor to submit data (arguments) that could resolve the Agency's concerns. If the sponsor can make a prima facie case that the issues identified by the Agency are resolvable, then perhaps an approvable letter or 3 month extension of the review clock (major amendment) are possible. Novartis said they would submit additional data (arguments) as far in advance of the October 17, 2004 action date as possible.

Minutes Preparation:

Edward Fromm

Concurrence, Chair:

Norman Stockbridge, M.D., Ph.D.

Drafted: ef/9/13/04

Final: ef/9/13/04

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

/s/

Norman Stockbridge
9/13/04 03:27:44 PM

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END=SEP-13 15:43

FILE NO. =608

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-FDA, CDER, OND, ODEI, DCRDP -

***** -CARDIO RENAL - ***** 301 594 5494- *****

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



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5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

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Transmitted to FAX Number: (973) 781-3590

Attention: Ms. Nancy Price

Company Name: Novartis Pharmaceuticals

Phone: (862) 778-3591

Subject: Minutes of Telecon w/FDA, September 9, 2004
NDA 21-283/S-011
Diovan (valsartan) Tablets

Date: September 13, 2004

Pages including this sheet: 4

From: Edward Fromm

Phone: 301-594-5328

Fax: 301-594-5494

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

Minutes of a Telephone Conference Call between Novartis and the FDA

Date: October 7, 2004

Application: NDA 21-283/S-011
Diovan (valsartan) Tablets

Sponsor: Novartis Pharmaceuticals, Inc.

Subject: Review of VALIANT Trial

FDA Participants

Norman Stockbridge, M.D., Ph.D., HFD-110, Acting Director, Division of Cardio-Renal Drug Products
Shari Targum, M.D., HFD-110, Acting Medical Team Leader
James Hung, Ph.D., HFD-710, Team Leader, Statistics
Konstantinos Ziogas, M.D., HFD-110, Visiting Scientist, EMEA
Lance McIeroy, HFD-42, Senior Regulatory Review Officer
Cheryl Ann Borden, HFD-110, MSN, RN, Regulatory Health Project Manager
Edward Fromm, HFD-110, Chief, Project Management Staff

Novartis

Marc Pfeffer, M.D., - VALIANT Study Chairman, Harvard Medical School
Francis Plat, M.D. - Executive Director, Cardiovascular CD&MA
Angelo Trapani - Clinical Research Manager, Cardiovascular CD&MA
Tom Chiang, Ph.D. - Director, Biostatistics and Statistical Reporting
Jim Gong, Ph.D. - Associate Director, Biostatistics and Statistical Reporting
Robert Glazer, M.D., Executive Director, Cardiovascular CD&MA
Malcom MacNab, M.D., Ph.D., Vice President, Cardiovascular CD&MA
William Daley, Executive Director, Cardiovascular CD&MA
Math Hukkelhoven, Ph.D. - Global Head, Drug Regulatory Affairs
Adrian Birch - Executive Director, Drug Regulatory Affairs
Nancy Price - Director, Drug Regulatory Affairs
Robert Califf, M.D., - VALIANT Executive Committee; Director, Duke Clinical Research Institute

Background

NDA 21-283/S-001, submitted on December 17, 2003, contains the results of the VALIANT (VALsartan In Acute myocardial infarction) trial, a randomized, controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and signs, symptoms or radiological evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction.

In response to a request from the Division during a teleconference on September 9, 2004, Novartis submitted on October 1, 2004, additional data to support their claim that valsartan is an acceptable alternative to an ACE inhibitor in patients who have experienced a myocardial infarction (MI).

Telecon

Dr. Stockbridge opened the telecon by noting that we have reviewed the sponsor's submission of October 1, 2004, but unfortunately have not been able to reach agreement on the approvability of the application. To permit a more substantial review of this submission and other VALIANT data, we are considering the submission of October 1, 2004 a major amendment. Therefore, the review clock will be extended by 3 months.

Dr. Stockbridge noted that data the sponsor submitted on the use of beta-blockers and ACE inhibitors was comforting, but we are still concerned that the pooling of the 3 studies (AIRE, TRACE, SAVE) was overestimating the effect of captopril. He noted that the Agency is struggling with how to narrow the CI (Confidence Level) of the ACE inhibitor effect without concomitantly pooling the nominal effect of the 3 trials. Novartis noted that they believe that SAVE alone can be used to justify the effect of captopril, as the numerical point estimate and CI largely overlap. Novartis also noted that the doses of beta blockers in the VALIANT trial were high and this may have contributed to the obscuring of the captopril effect in the study.

Dr. Stockbridge asked about the derivation of Figure 1 (Kaplan-Meier estimates for all-cause mortality in SAVE by beta-blocker use and treatment) in the sponsors October 1st submission. Novartis replied that the curves in Figure 1 were derived from SAVE alone and were for Beta Blocker use at baseline. Dr. Stockbridge said it would be helpful to do calculations about Beta Blocker use at baseline with the other studies as well (TRACE and AIRE). Novartis said they would submit this data to the Division.

Novartis asked if there were any issues pertaining to the VALIANT study the Agency was prepared to discuss. Dr. Stockbridge said there were none at this time, but noted we would be open to meetings or telecons with the sponsor as necessary during the extended review period.

Summary of Main Action Items

- Novartis will provide additional data regarding baseline Beta Blocker use for the TRACE and AIRE studies.
- The Division will setup meetings or telecons as necessary during the 3 month extended review period.
- The Division will send an acknowledgement letter for the 3 month extension of the user fee clock to January 17, 2005.

Minutes Preparation:

Edward Fromm

Concurrence, Chair:

Norman Stockbridge, M.D., Ph.D.

Drafted: ef/10/15/04-10/22/04

Final: CABorden-10/19/04
LMcleroy-10/18/04
JHung-10/21/04
STargum- 10/21/04
NStockbridge-10/21/04

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/s/

Norman Stockbridge
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ATTACHMENT

MEMO OF FILING MEETING (January 29, 2004)

BACKGROUND:

This efficacy supplement, submitted on December 17, 2003, contains the results of the VALIANT (VALsartan In Acute myocardial iNfarction) trial, a randomized, controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and signs, symptoms or radiologic evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction. Novartis believes that valsartan in the overall VALIANT study population, demonstrated equivalent efficacy to captopril. They also believe that valsartan was shown to be efficacious and safe in post-myocardial infarction patients who did not receive ACE inhibitor therapy.

Clinical investigations of Diovan for the treatment of post myocardial infarction in the United States were conducted under IND 40,783.

ATTENDEES:

Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Thomas Marciniak, M.D., HFD-110, Medical Team Leader
Shari Targum, M.D., HFD-110, Medical Officer
Nhi Nguyen, Pharm.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Anthony Proakis, Ph.D., HFD-110, Pharmacologist
Stuart Zimmerman, Ph.D., HFD-810, Chemist
Robert Shibuya, Ph.D., HFD-45, DSI, Pharmacologist
Jackie O'Shaughnessy, Ph.D., HFD-48, DSI/GLP and Bioequivalence
Nilufer Tampal, Ph.D., HFD-48, Toxicologist (for CT Viswanathan)
Zelda McDonald, HFD-110, Chief, Project Management Staff
Edward Fromm, HFD-110, Regulatory Health Project Manager

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>	<u>Expected</u>
Medical	Shari Targum, M.D.	July 1, 2004
Secondary Medical:	TBD	
Statistical:	James Hung, Ph.D.	July 1, 2004
(note: a joint Med/Stat review will be done for this application)		
Pharmacology:	Anthony Proakis, Ph.D.	No review required,
but memo will be put into DFS and labeling sent to Jeri El-Hage for review		
Statistical Pharmacology:	NA	
Chemist:	Stuart Zimmerman, Ph.D.	July 1, 2004
Environmental Assessment:	Stuart Zimmerman, Ph.D.	July 1, 2004
Clinical Pharmacology & Biopharmaceutics:	Nhi Nguyen, Pharm.D.	July 1, 2004
Microbiology:	NA	
DSI (clinical):	Robert Shibuya, Ph.D.	TBD
DSI (GLP):	NA	NA
Project Manager:	Edward Fromm	
Other Consults:	NA	

Per reviewers, all parts in English, or English translation? YES NO

CLINICAL – File Refuse to file

• Clinical site inspection needed: YES TBD NO

MICROBIOLOGY CLINICAL – File NA Refuse to file

STATISTICAL – File Refuse to file

BIOPHARMACEUTICS – File Refuse to file

• Biopharm. inspection Needed: YES NO

PHARMACOLOGY – File Refuse to file

CHEMISTRY –

• Establishment(s) ready for inspection? YES NO File Refuse to file
(no inspections needed for this efficacy supplement)

REGULATORY CONCLUSIONS/DEFICIENCIES:

The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

No filing issues have been identified.

Filing issues to be communicated by Day 74.

ACTION ITEMS:

- Filing issues/no filing issues will be documented and conveyed to applicant in the 74-Day letter by February 29, 2004
- Dr. Targum noted that she has been unable to locate the database for the trials (SAVE, AIRE, & TRACE) that were used to calculate the non-inferiority margin in the trial. In addition, minutes of the DSMB will be requested from the sponsor to see if results of the interim analyses influenced the outcome of the trial.
- An internal meeting will be held in 7-14 days to discuss whether an Advisory Committee Meeting should review this application. In addition, the concerns identified above by Dr. Targum will be readdressed.

Mr. Edward Fromm
Regulatory Project Manager, HFD-110

Rd:

JO'Shaughnessy-2/12/04
ZMcDonald-2/18/04
NTampal-2/18/04
RShibuya-2/18/04
KSrinivasachar-2/17/04

STargum-2/23/04
SZimmerman-2/23/04
AProakis-2/23/04
NBeasley-2/23/04
JHung-2/23/04

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2-18-04

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA 21-283/S-011, Diovan (valsartan) Tablets, 40, 80, 160, and 320 mg

Applicant: Novartis Pharmaceuticals

Date of Application: December 17, 2003

Date of Receipt: December 17, 2003

Date of Filing Meeting: January 29, 2004

Filing Date: February 15, 2004

74 day ltr due: February 29, 2004

Indication(s) requested: Reduction in cardiovascular and total mortality following myocardial infarction. Novartis believes that in the overall VALIANT study population, valsartan demonstrated equivalent efficacy to captopril. They also believe that valsartan was shown to be efficacious and safe in post-myocardial infarction patients who did not receive ACE inhibitor therapy.

Type of Application: Full NDA _____ Supplement X
(b)(1) X (b)(2) _____

Therapeutic Classification: Standard (10 month)

Resubmission after a withdrawal or refuse to file NA

Chemical Classification: (1,2,3 etc.) 6

Other (orphan, OTC, etc.) NA

Has orphan drug exclusivity been granted to another drug for the same indication? NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? NO

If the application is affected by the application integrity policy (AIP), explain. NO

User Fee Status: Paid X Waived (e.g., small business, public health) _____

Exempt (orphan, government) NA

Form 3397 (User Fee Cover Sheet) submitted: YES X NO _____

User Fee ID# 4622

Clinical data? YES X NO _____ Referenced to NDA# _____

Date clock started after UN NA

User Fee Goal date: October 17, 2004

Action Goal Date (optional) October 17, 2004

- Does the submission contain an accurate comprehensive index? YES
- Form 356h included with authorized signature? YES
If foreign applicant, the U.S. Agent must countersign.
- Submission complete as required under 21 CFR 314.50? YES
- If electronic NDA, does it follow the Guidance? NA

If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Technical Document, does it follow the guidance? NA
- Patent information included with authorized signature? YES
- Exclusivity requested? NO; If yes, ___ years

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES
If foreign applicant, the U.S. Agent must countersign.

Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. 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 the studies listed in Appendix ____." Applicant may not use wording such as, "To the best of my knowledge,"

- Financial Disclosure included with authorized signature? YES
(Forms 3454 and/or 3455)
If foreign applicant, the U.S. Agent must countersign.
- Has the applicant complied with the Pediatric Rule for all ages and indications? NO, but waiver granted by Division
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

List referenced IND numbers: IND 40,783

End-of-Phase 2 Meeting? April 29, 1996
Pre-NDA Meeting(s)? September 16, 2003

Project Management

Copy of the labeling (PI) sent to DDMAC? YES

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support? NA

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support? NA

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? NA

Advisory Committee Meeting needed? TBD

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NA

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES
 If no, did sponsor submit a complete environmental assessment? NA
 If EA submitted, consulted to Nancy Sager (HFD-357)? NA
- Establishment Evaluation Request (EER) package submitted? NA
- Parenteral Applications Consulted to Sterile Products (HFD-805)? NA

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-283/S-011

FILING COMMUNICATION

2/25/04

Novartis Pharmaceuticals
Attention: Ms. Nancy A. Price
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Ms. Price:

Please refer to your supplemental new drug application (NDA) dated December 17, 2003, received December 17, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diovan (valsartan) 40, 80, 160, and 320 mg Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 15, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

CMC

- Please clearly summarize all the CMC changes relative to what is approved for the 40 mg tablet.
- Please provide annotated specifications and related control documents (e.g., stability specifications and batch records) showing all the necessary changes (e.g., tablet description).
- Please confirm that you plan to carry out physical testing (e.g., disintegration, hardness, loss on drying, etc.) in a similar manner akin to the current 40 mg tablet.

We are providing the above comments to give you preliminary notice of potential review issues. Submission of data relevant to these identified deficiencies is solicited to further the review. As the review of the NDA is not complete, this is not indicative of deficiencies that may be identified with a completed review. Issues may be added, deleted, expanded upon, or modified with a complete review of the submission.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doug Throckmorton
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Minutes of a Meeting between Novartis and the FDA

Date: December 17, 2004

Application: NDA 21-283/S-011
Diovan (valsartan) Tablets

Sponsor: Novartis Pharmaceuticals, Inc.

Subject: Review of VALIANT Trial

FDA Participants

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation I
Norman Stockbridge, M.D., Ph.D., HFD-110, Acting Director, Division of Cardio-Renal Drug Products
Thomas Marciniak, M.D., HFD-110, Medical Team Leader
Shari Targum, M.D., HFD-110, Acting Medical Team Leader
James Hung, Ph.D., HFD-710, Team Leader, Statistics
Mehul Desai, M.D., HFD-110, Medical Officer
Khin Maung U, M.D., HFD-110, Medical Officer
Edward Fromm, HFD-110, Chief, Project Management Staff

Novartis

Marc Pfeffer, MD - VALIANT Study Chairman, Harvard Medical School
John McMurray, MD - VALIANT Study Co-Chairman, University of Glasgow, UK
Scott Solomon, MD - VALIANT Clinical End-Point Committee Chairman, Brigham & Women's Hospital, Harvard Medical School
Gary Koch, PhD - Biostatistician, University of North Carolina
Francis Plat, MD - Executive Director, Cardiovascular Clinical Development & Medical Affairs (CD&MA)
Angelo Trapani - Clinical Research Manager, Cardiovascular CD&MA
Robert Glazer, MD - Executive Director, Cardiovascular CD&MA
Malcolm MacNab, MD, PhD - Vice-President, Cardiovascular CD&MA
William Daley, MD - Executive Director, Cardiovascular CD&MA
Tom Chiang, PhD - Director, Biostatistics and Statistical Reporting
Jim Gong, PhD - Associate Director, Biostatistics and Statistical Reporting
Math Hukkelhoven, PhD - Global Head, Drug Regulatory Affairs
Adrian Birch - Executive Director, Drug Regulatory Affairs
Nancy Price - Director, Drug Regulatory Affairs
Soraya Madani - FDA Liaison, Drug Regulatory Affairs

Background

NDA 21-283/S-011, submitted on December 17, 2003, contained the results of the VALIANT (VALsartan In Acute myocardial iNfarction) trial, a randomized, controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and signs, symptoms or radiological evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction.

In response to a request from the Division during a teleconference on September 9, 2004, Novartis submitted on October 1, 2004, additional data to support their claim that valsartan is an acceptable alternative to an ACE inhibitor in patients who have experienced a myocardial infarction (MI). The Division considered this submission a major amendment with the review clock being extended by 3 months. The new goal date for the application is January 17, 2005.

In response to a request from the Division on October 9, 2004, Novartis submitted additional information regarding the use of beta-blockers in the VALIANT study. The meeting today is to discuss this submission as well as the overall progress of the review of the application.

Meeting

Dr. Temple opened the meeting by noting that the information submitted regarding beta-blocker use in the VALIANT trial was reassuring. Although the use of beta-blockers is much greater in the new trial, it appears that ACEIs have a good effect in the presence of beta blockers. He noted that at a previous meeting we said that use of all 3 studies (SAVE, AIRE, TRACE) as a basis for estimating the control group effect was acceptable, given that the sponsor would use the lower (worst) 95% bound of the CI for the mortality effect to calculate the non-inferiority margin. Although somewhat arbitrary, a non-inferiority margin of 1.13 was chosen by the sponsor, representing 50% retention of the point estimate of the mortality effect of captopril.

Dr. Temple noted that we believe that use of the 95% lower bound of the CI for the pooled data to represent captopril's effect is conservative but that selecting a non-inferiority margin based on the point estimate of captopril's effect is not conservative. From our perspective, it appears that the non-inferiority margin that can be ruled out is about 1.108, indicating about 36% retention of captopril's effect. This is not so far from our expectations and therefore we believe that this drug is appropriate for this indication in an ACE intolerant population.

Novartis replied that they believe that their data not only support the use of the drug in an ACE intolerant population, but in fact as a substitute for an ACE inhibitor in this indication. The firm presented a slide that shows that valsartan preserves more than 50% of the mortality benefit of captopril, based on the lower bound of the 95% CI. They believe this result is even more pronounced using a per-protocol analysis of the data. Dr. Temple replied that the firm should expand on the argument that the ITT and per-protocol analysis retain 50% of the mortality effect and submit this to the Division for review.

Novartis noted that the VALIANT trial was really 2 separate trials combined into one, but with one control (captopril). They believe that the multiplicity assessment factored into these trials was excessive and reduced the true preservation of the mortality effect in the trial. Novartis also argued that an adjustment of the data factoring in the high use of beta-blockers in the trial (70%), in effect raises the preservation rate to around 70%. Dr. Temple said that firm should detail these arguments further in a submission to the Division.

Novartis presented a slide that detailed the secondary endpoints of the study (e.g., CV Death, CV Death or Heart Failure, and CV Death, ReMI, or Heart Failure) and noted that as the class of CV events are broadened, the point estimates shift more to the left and the non-inferiority margin becomes more reassuring. Dr. Temple invited the firm to expand these arguments for both the 95 and 97.5% CIs.

Novartis asked what additional arguments are needed to buttress their view that captopril was the best control for this study. Dr. Temple replied that it appears that captopril is associated with the smallest effect size and due to the dosing regimen for the drug, missed doses are of potential concern with the drug.

The firm noted that they believe captopril was an appropriate control for the trial, especially given the early date of initiation of the study. Dr. Temple said that the firm can submit arguments that validate the robustness of the data in the trial.

Dr. Stockbridge requested that the raw (source) data from the SAVE trial be sent to the Division for review. Novartis said they would send these data as soon as possible.

Summary of Main Action Items

Dr. Temple said he believes there is a path to approval for this supplement, at least for patients who are intolerant to ACE inhibitors. Novartis argued that valsartan should really be a substitute for ACE inhibitors for this indication and will submit the following information to the Division:

1. Multiplicity adjustment for the same control (captopril) is excessive
2. A per-protocol analysis of the data that shows a higher retention of mortality effect of captopril
3. An adjustment for the high beta-blocker use in the trial results in a higher preservation of the captopril effect.
4. CV secondary endpoints in the trial all point in the right direction and are supportive of the non-inferiority margin chosen by the firm.
5. Raw (source) data from the SAVE trial.
6. Other data that can argue for the robustness of the trial results.

Minutes Preparation:

Edward Fromm

Concurrence, Chair:

Robert Temple, M.D.

Drafted: ef/12/28/04-1/7/05

Final: RTemple-1/7/05
NStockbridge-1/4/05
TMarciniak- 1/4/05
STargum- 1/3/05
JHung-1/3/05
MDesai- 1/3/05
KU-12/28/04

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Table 2 Preservation (%) of mortality benefit of captopril to be provided by valsartan (based on the method proposed by Vic Hasselblad and David F. Kong, Drug Information Journal, Vol. 35, pp. 435-449, 2001)

Historical reference for mortality benefit of captopril/ACE inhibitor	% preservation of mortality benefit provided by valsartan, (95% confidence interval)	
	ITT population	Per-protocol population
Both estimate and variability of effect size from meta analysis of SAVE, AIRE, and TRACE trials	99.6% (65.1%, 134.1%) [included in the original submission]	108.3% (69.7%, 146.8%)
Both estimate and variability of effect size from SAVE alone	99.5% (57.2%, 141.8%)	110.1% (62.3%, 157.9%)

The results above indicate that valsartan preserves more than 50% of mortality benefit of captopril/ACE inhibitor, based on the lower bounds of the 95% confidence intervals.

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4. Strong non-inferiority results were obtained for the pre-specified secondary endpoints

ITT population

Endpoint	Trt	Death (%)	Hazard Ratio	One-sided 97.47% CI	P-value* for non-inf
CV mortality	Val	827/4909 (16.8)	0.976	0 – 1.075	0.0014
	Cap	830/4909 (16.9)			
CV mortality, hospitalization for HF, MI	Val	1529/4909 (31.1)	0.955	0 – 1.024	<0.0001
	Cap	1567/4909 (31.9)			
CV mortality, hospitalization for HF, MI, stroke, sudden cardiac arrest with resuscitation	Val	1612/4909 (32.8)	0.961	0 – 1.029	<0.0001
	Cap	1641/4909 (33.4)			

*Non-inferiority p-value was calculated according to the pre-defined threshold of 1.13

Per-protocol population

Endpoint	Trt	Death (%)	Hazard Ratio	One-sided 97.47% CI	P-value* for non-inf
CV mortality	Val	681/4764 (14.3)	0.961	0 – 1.069	0.0014
	Cap	688/4770 (14.4)			
CV mortality, hospitalization for HF, MI	Val	1356/4764 (28.5)	0.957	0 – 1.032	<0.0001
	Cap	1376/4770 (31.9)			
CV mortality, hospitalization for HF, MI, stroke, sudden cardiac arrest with resuscitation	Val	1437/4764 (30.2)	0.968	0 – 1.041	<0.0001
	Cap	1443/4770 (30.3)			

*Non-inferiority p-value was calculated according to the pre-defined threshold of 1.13

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§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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/s/

Robert Temple
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Minutes of a Meeting between Novartis and the FDA

Date: January 12, 2005

Application: NDA 21-283/S-011
Diovan (valsartan) Tablets

Sponsor: Novartis Pharmaceuticals, Inc.

Subject: Update on Regulatory Action for the VALIANT Study

FDA Participants

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation I (pre-meeting only)
Norman Stockbridge, M.D., Ph.D., HFD-110, Acting Director, Division of Cardio-Renal Drug Products
Thomas Marciniak, M.D., HFD-110, Medical Team Leader
Shari Targum, M.D., HFD-110, Acting Medical Team Leader
James Hung, Ph.D., HFD-710, Team Leader, Statistics
Khin Maung U, M.D., HFD-110, Medical Officer
Edward Fromm, HFD-110, Chief, Project Management Staff

Novartis

Francis Plat, MD – Executive Director, Cardiovascular Clinical Development & Medical Affairs (CD&MA)
Angelo Trapani – Clinical Research Manager, Cardiovascular CD&MA
Robert Glazer, MD - Executive Director, Cardiovascular CD&MA
Malcolm MacNab, MD, PhD - Vice-President, Cardiovascular CD&MA
Ameet Nathwani, MD – Head, Cardiovascular CD&MA
Tom Chiang, PhD – Director, Biostatistics and Statistical Reporting
Adrian Birch – Executive Director, Drug Regulatory Affairs
Nancy Price – Director, Drug Regulatory Affairs
Chin Koerner - FDA Liaison, Drug Regulatory Affairs

Background

NDA 21-283/S-011, submitted on December 17, 2003, contained the results of the VALIANT (VALsartan In Acute myocardial infarction) trial, a randomized, active-controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and signs, symptoms or radiological evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction.

In response to a request from the Division during a teleconference on September 9, 2004, Novartis submitted on October 1, 2004, additional data to support their claim that valsartan is an acceptable alternative to an ACE inhibitor in patients who have experienced a myocardial infarction (MI). The Division considered this submission a major amendment with the review clock being extended by 3 months. The new goal date for the application is January 17, 2005.

The meeting today is to discuss this submission as well as the overall progress of the review of the application and the upcoming regulatory decision from the FDA.

Meeting

Dr. Stockbridge opened the meeting by noting that although Dr. Temple could not be present for the meeting, he and the Division find the evidence from the VALIANT trial support valsartan for post myocardial infarction in patients who are intolerant of ACE inhibitors. Although persuasive arguments have been made by the applicant for use of valsartan as a substitute for ACE inhibitors in this condition, the constancy assumption used for comparing the VALIANT database with the SAVE, AIRE, and TRACE data was problematic, because in the AIRE and TRACE trials, an ACE inhibitor other than captopril was used. Dr. Stockbridge said the Agency was comforted about the beta-blocker use in the VALIANT trial, but there was still anxiety about giving an unrestricted claim based on non-inferiority margin when no placebo was present. Nevertheless, Dr. Stockbridge encouraged the sponsor to have a meeting with Dr. Temple in the near future, and at that time make arguments that the results of VALIANT are clinically relevant when compared to the other study databases and support the use of valsartan as an alternative to ACE inhibitors in this patient population.

Dr. Stockbridge noted that the presentation of the secondary endpoints in the VALIANT trial in the labeling should account for the effect of captopril as was done with the primary endpoints in the study. Thus, context for these endpoints would be needed from the SAVE, AIRE, and TRACE trials. This information could also be helpful in supporting the firm's contention that valsartan is interchangeable for an ACE inhibitor in patients post myocardial infarction. Novartis replied that there were no cardiovascular deaths in the other 3 trials, so this comparison will be difficult. They noted that they believe the secondary endpoints in the trial strengthen the CI in the trial and make the non-inferiority margin more reassuring.

Regulatory Action

Dr. Stockbridge said we are prepared to issue by the January 14, 2005, an approval letter based on draft labeling for valsartan in patients post-myocardial infarction who are intolerant to ACE inhibitors. Nevertheless, we are also open to issuing an approvable letter for this indication to give the sponsor more time to make arguments to Dr. Temple that the results of VALIANT are clinically relevant when compared to the other study databases and support the use of valsartan as an alternative to ACE inhibitors in this patient population. Novartis said it was their preference to receive an approvable letter at this stage of the review process, and to have a meeting with Dr. Temple in the near future to present arguments as to why valsartan should be a substitute for an ACE inhibitor in this patient population.

Summary of Main Action Items

1. The Division will issue an approvable letter by January 14, 2005, for the use of valsartan in patients post myocardial infarction who are intolerant to ACE inhibitors.
2. Novartis will have a meeting with the Division and Dr. Temple to present arguments about the clinical relevance of the VALIANT data in supporting valsartan as interchangeable with an ACE inhibitor in patients post myocardial infarction.
3. Novartis will try to obtain historical context data with respect to captopril for the secondary endpoints in the VALIANT trial to include these endpoints in the labeling as well as to support the use of valsartan as a substitute for ACE inhibitors in this condition.

Minutes Preparation:

Edward Fromm

Concurrence, Chair:

Norman Stockbridge, M.D., Ph.D.

Drafted: ef/1/25/05-2/8/05

Final: NStockbridge-2/7/05
TMarciniak- 2/7/05
STargum- 2/7/2005
JHung- 2/5/2005
KMahjoob-2/7/2005

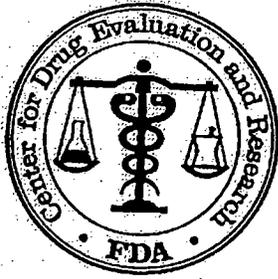
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/s/

Norman Stockbridge
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DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 21-283 Valsartan

Sponsor: Novartis

Submission: SE1-011 (17 December 2003): a request to approve valsartan for use post myocardial infarction.

Review date: 13 January 2005

From: N. Stockbridge, M.D., Ph.D., Acting Director, HFD-110

Distribution: NDA 21-283
HFD-110/Project Manager
HFD-710/Hung
HFD-110/Targum
HFD-110/Marciniak

This memo conveys the Division's regulatory decision for NDA 21-283 supplement 011 (received 17 December 2003), which provides for a new labeling claim based on the VALIANT study. This study was reviewed by Drs. Targum and Hung in a joint review dated 30 June 2004 and in a subsequent addendum by Dr. Hung (not yet DFS). There is no chemistry, pharmacology, clinical pharmacology, or biopharmaceutical issue.

The sponsor seeks the following claim

VALIANT was a double-blind, parallel group study in which 14,803 subjects (at 931 centers in 24 countries) with a recent myocardial infarction (12 h to 10 d) and heart failure or left ventricular dysfunction were randomized to captopril (titrated to a target dose of 50 mg tid), valsartan (titrated to a target dose of 160 mg bid), or the combination of valsartan and captopril (target dose of 80 bid/50 tid) and followed for time to all-cause mortality until there were 2700 events.

The study had two primary hypotheses, superiority of the combination over captopril and superiority of valsartan alone over captopril. Were valsartan not superior to captopril, a "non-inferiority" comparison was to follow. After adjustments are made for multiple comparisons and for several planned and executed interim analyses, each comparison was considered significant at $\alpha < 0.0253$.

The study appears to have been generally well designed and executed; however, one Eastern European site was dropped for inadequate documentation. Fewer than 5% of

subjects withdrew from treatment and vital status was known for 99.6% of all subjects randomized.

The population was 31% female, 94% Caucasian, and the median age was 65. Common medical history included smoking (63%), hypertension (55%), angina (40%), prior MI (28%), dyslipidemia (29%), diabetes (23%), unstable angina (21%), and CHF (15%). The mean ejection fraction was about 35%. Common medications at baseline included aspirin (91%), beta-blocker (71%), heparin (52%), diuretic (50%), nitrate (44%), ACE inhibitor (40%), and statin (34%). Twenty-one percent of subjects were on open-label ACE inhibitors during treatment.

Neither potential superiority claim is supported by the findings (p=0.98 for valsartan alone and p=0.73 for the combination). The findings for "non-inferiority" are more difficult to interpret.

The sponsor's analysis of the reference effect of captopril was based on three studies of mortality in subjects considered to be a similarly high risk studied in the post MI setting. These studies were SAVE (captopril), AIRE (ramipril), and TRACE (trandolapril). The sponsor's analyses weighted the studies equally.

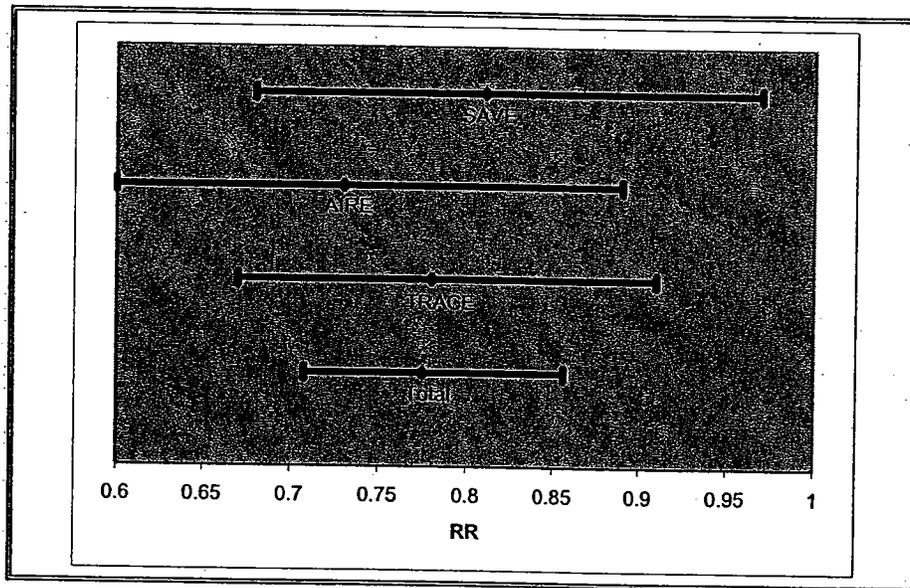


Figure 1. Setting the margin for VALIANT

The sponsor chose to preserve 50% of the nominal reference effect, 0.773. Ordinarily, one could have determined the upper bound of the $\frac{V}{C}$ confidence limit to ensure that

$$\frac{V}{P} \text{ preserved an effect of } 50\% \times (1 + 0.773) \text{ and solving for } \frac{V}{C} = \frac{\frac{V}{P}}{\frac{C}{P}} = \frac{0.8875}{0.773} = 1.147,$$

but the sponsor used a somewhat more conservative boundary of 1.13, which preserves about 55.7% of the estimated nominal effect, to enable VALIANT to show that valsartan was better than placebo by total loss of the upper bound of the reference ACE inhibitor effect. At the time the VALIANT protocol was reviewed, the Agency recommended (review by Dr. Ganley of 7/22/1998) that the "non-inferiority" margin be set at a still more conservative level of 1.09, based on a "worst 95% CI" analysis.

In addition, the sponsor intended and performed the “non-inferiority” analysis as a one-sided test, but the reviewers argue that two-sided testing is necessary so that all the superiority and “non-inferiority” tests use the same confidence interval and thereby avoid further correction for multiplicity.

Other variations on the planned mortality analysis are summarized in the table below.

Table 1. Mortality analyses in VALIANT

Studies compared	Method	Includes variance?	CI width	Result CI	50% margin	Success?
SAVE + AIRE + TRACE	Point estimate	No	97.47%	0.904, 1.108	1.13	Yes
	Worst CI (0.856)	Yes	97.47%	0.904, 1.108	1.08	No
	Synthesis	Yes	(wider)	0.890, 1.125	1.13	No
SAVE + AIRE	Worst CI (0.879)	Yes	97.47%	0.904, 1.108	1.067	No
	Synthesis	Yes	(wider)	0.881, 1.137	1.14	Yes
SAVE	Worst CI (0.97)	Yes	97.47	0.904, 1.108	1.02	No
	Synthesis	Yes	(wider)	0.866, 1.157	1.111	No

Analyses based on 3 reference studies included SAVE, AIRE, and TRACE. Of these, TRACE is an outlier with respect to the number of events observed, a difference that does not appear to be explained by duration of follow-up. Analyses based on 2 studies excluded TRACE. Analyses for one reference study were based on SAVE, the only study to use captopril.

A major concern in “non-inferiority” analyses is whether the reference treatment retains its historically established effect, the “constancy assumption”. For this reason, comparisons are based on relative risk, expecting that is less likely to erode than is absolute magnitude of benefit. In the case of captopril, concern about the constancy assumption was fueled by the increasing use of beta-blockers in the years since SAVE and the observation in Val-HeFT that beta-blocker usage with valsartan was adverse. To address this specific concern, the sponsor provided analyses of SAVE subset by beta-blocker usage. These results, confirmed in Dr. Hung’s addendum, suggest that beta-blocker use had additive benefits on top of captopril. Neither result (SAVE or Val-HeFT) was obtained with randomization to beta-blockers, so the quality of insight based on these observations is equally bad.

Because of general concerns about the constancy assumption, one conservatively chooses a target margin in conjunction with a target alpha. This, to a greater or lesser extent, protects one against changes in the magnitude of the effect of the reference treatment, but it does nothing to protect against the possibility that the reference treatment no longer contributes at all or is actually adverse.

Conventionally, “non-inferiority” studies have a hypothesis involving preservation of some fraction, usually 50%, of the reference effect. While preservation of 50% cannot be described as truly non-inferior, one knows that the true effect is often likely to be somewhat larger than this lower bound. However, one can be assured (with a small p-value) of 50% preservation and be equally assured that as much as, say, 75% has not been preserved. Thus, the typical “non-inferiority” hypothesis focuses attention on a single point in what is a continuous relationship between the fraction of the reference effect size that has been preserved and the degree of assurance that this is so. This entire continuous relationship is based on the same set of observations and thus requires no adjustment for multiplicity.

I go through the development of the whole preservation curve below, but I note that better reference points for positive-controlled studies are the reference effect and the zero-effect level. In the former case, one need only assume the reference effect is not adverse, so superiority can be assessed at alpha levels similar to placebo-controlled studies. In the latter case, a much lower α -value is needed to afford protection against inconstancy (in magnitude) and such a result is readily interpretable as true non-inferiority (no quotation marks) to placebo.

While the sponsor's analysis plan based estimates of the effect of the reference treatment on the point estimates of the effects in SAVE, AIRE, and TRACE, Dr. Hung's review employs the "synthesis method", which factors in the variance observed in the reference studies¹.

Dr. Hung has shown that the synthesis method can be written as

$$\exp\left(\log\left(\frac{\hat{V}}{\hat{C}}\right) + \kappa \sqrt{\text{var}\left(\log\left(\frac{\hat{V}}{\hat{C}}\right)\right) + (1-\phi)^2 \text{var}\left(\log\left(\frac{\tilde{C}_0}{\tilde{P}_0}\right)\right)}\right) < \exp\left(- (1-\phi) \log\left(\frac{\tilde{C}_0}{\tilde{P}_0}\right)\right)$$

where ϕ is the fraction of the effect being preserved and κ takes on values {1.65, 1.96, 2.237, 2.58, 3.72} corresponding to α in {0.1, 0.05, 0.0257, 0.01, 0.00125}. This is of the same form, but somewhat more general than the equation on page 50 of the joint medical-statistical review. (Other terms have the same meaning as described in that review.)

This can be rewritten in the following form

$$\frac{\log\left(\frac{\hat{V}}{\hat{C}}\right) + (1-\phi) \log\left(\frac{\tilde{C}_0}{\tilde{P}_0}\right)}{\sqrt{\text{var}\left(\log\left(\frac{\hat{V}}{\hat{C}}\right)\right) + (1-\phi)^2 \text{var}\left(\log\left(\frac{\tilde{C}_0}{\tilde{P}_0}\right)\right)}} < -\kappa$$

The left-hand side is the synthesis test, compared with the so-called critical value $-\kappa$ that corresponds to an alpha level. When this inequality holds, one can conclude at that alpha level of statistical significance that valsartan preserves the fraction ϕ of the control's effect. If κ is substituted by the value of the synthesis test on the left-hand side, then it corresponds to the p-value (one-sided) of the test.

Thus, with values of $\frac{\tilde{C}_0}{\tilde{P}_0}$ and $\text{var}\left(\log\left(\frac{\tilde{C}_0}{\tilde{P}_0}\right)\right)$ known from historical data and $\frac{\hat{V}}{\hat{C}}$ and $\text{var}\left(\log\left(\frac{\hat{V}}{\hat{C}}\right)\right)$ known from VALIANT, this gives the degree of confidence (κ) one has that ϕ fraction of the effect of captopril has been preserved by valsartan.

The figure below shows the probability that valsartan fails to preserve any fraction of the historical effect of captopril.

¹ This method is not popular for power calculations because it requires it requires estimates of both the expected treatment magnitude and its variance.

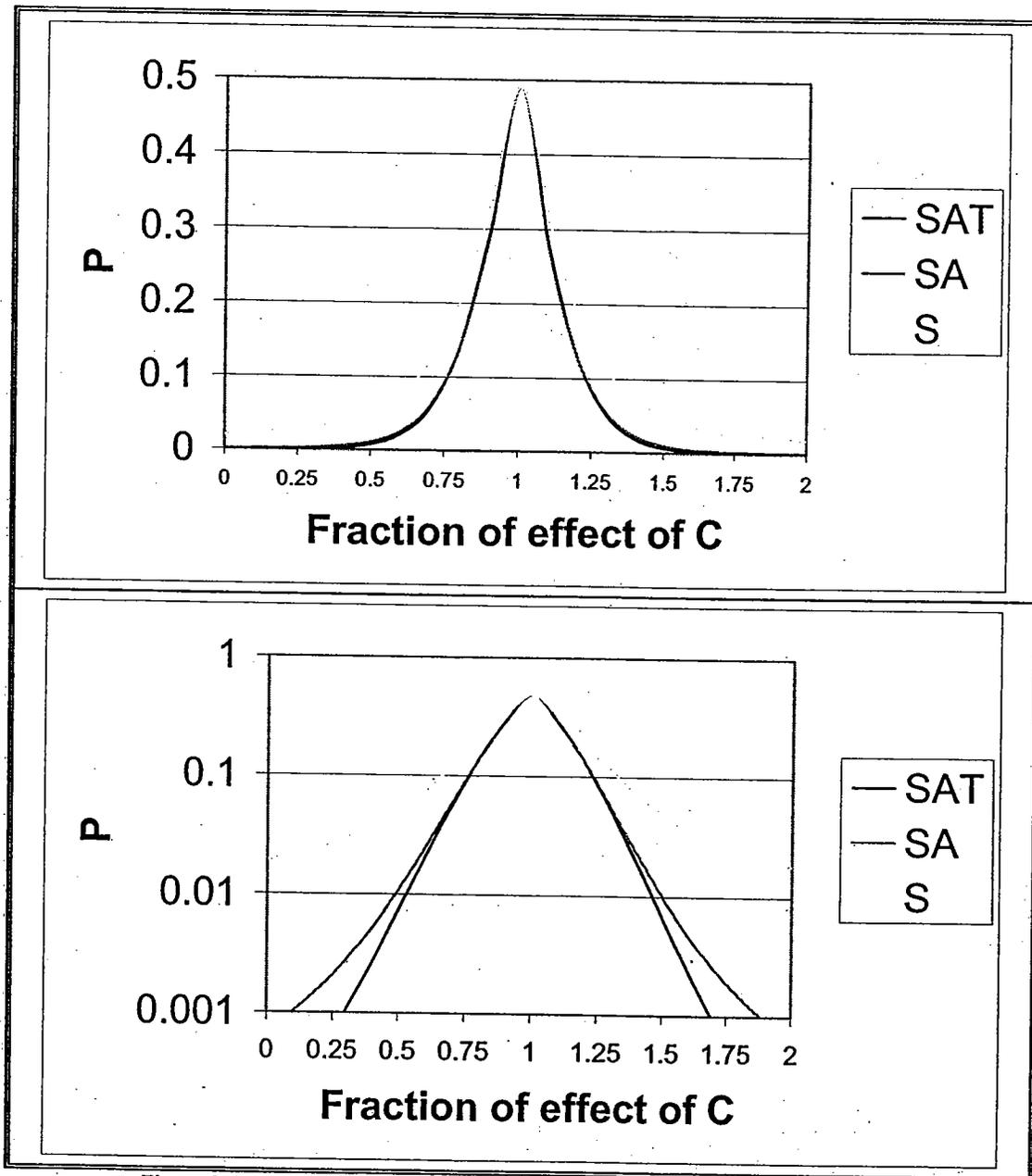


Figure 2. Probability that valsartan does not preserve some fraction of the effect of captopril based on SAVE only (S), SAVE plus AIRE (SA), or SAVE, AIRE, and TRACE (SAT). The probability axis is logarithmic in the lower panel.

Ignoring the constancy assumption for the moment, the observed relative risk of 1.001 corresponds to preservation of approximately 100% of the effect of captopril with a probability of about 0.5, as expected, and preservation of 75% of the captopril effect with a likelihood usually considered marginal. However, that valsartan would have been superior to placebo, i.e., that it preserves at least a small positive fraction of the effect of captopril, has a high likelihood (low p-value) based on at least SAVE plus AIRE, and it is pretty likely based on SAVE alone.

The unverifiable constancy assumption requires us to set a much lower alpha-level here than one would for a placebo-controlled study to achieve the same level of confidence in the overall result. How much lower it needs to be is a judgment, but there are two aspects of the constancy problem in VALIANT—the long time between the reference trials and VALIANT and cross-ACE inhibitor constancy (so one is allowed to use AIRE and TRACE). Specific concern about the interaction of captopril with beta-blockers was adequately addressed by the sponsor. To the extent one believes in the class effect, the general constancy-over-time issue is addressed somewhat by replication of findings with the other ACE inhibitors, but AIRE and TRACE are both nearly as old as SAVE. In short, if all one had as the basis for making this decision were the results of SAVE and VALIANT, I would not find it compelling that valsartan is superior to placebo, despite a nominal p-value (Figure 2) of about 0.02.

The additional assurance comes from AIRE and TRACE. The synthesis method gives one a formal way of incorporating them. With AIRE alone, the nominal p-value for superiority to placebo drops to 0.0007.

The sponsor points out that the analyses of the per-protocol population suggest greater preservation of the effect of captopril on mortality and that the alpha-splitting rule for VALIANT's two primary hypotheses was quite conservative. While true, these arguments do little, in my view, to balance the uncertainties of the constancy assumption.

If valsartan is judged adequately likely to be better than placebo, does that make it a first-line alternative to ACE inhibitor? One very good thing about placebo-controlled trials is that once gets an explicit estimate of the treatment effect size. We describe such estimates in the label because we expect physicians to use them in selecting therapy. Information about the absolute magnitude of effect size is missing here, and I am reluctant to grant labeling that makes the quality of the information here appear to be as good as, say, that of captopril.

These conclusions lead to labeling of valsartan in patients who cannot tolerate an ACE inhibitor, despite it having a most likely estimate of effect as large as that of captopril. I note that had a placebo-controlled study been conducted showing a benefit greater than placebo but smaller than historical estimates for ACE inhibitors, one probably would not have labeled valsartan for second-line use. While this seems a bit ironic, I think it is justified based on the uncertainties that have been factored into a decision based on a "non-inferiority" design.

It would be awkward to put a p-value in the label from any such calculation, because they would have to be qualified by many words describing constancy concerns. I note precedence for omitting the p-value in the XELODA label.

The all-cause and cardiovascular mortality curves for captopril, valsartan, and the combination are all superimposable. After Val-HeFT, apparent superiority of the combination would have been treated as something of a surprise, probably requiring a level of support greater than VALIANT could have provided. Effects were similar in subgroups based on demographics (age, gender, race), site location, baseline disease, characteristics of the index MI and CHF, and baseline medications or procedures.

Secondary analyses of the composite of cardiovascular death, recurrent MI, and CHF hospitalization also showed very similar effects in all 3 arms. Likewise "tertiary" analyses of all-cause hospitalization and cardiovascular morbidity showed strong similarity between the captopril and valsartan groups. However, the only sensible way to interpret these results is like what was done for the primary end point, by estimating the historical effects for the reference treatment, making assumptions about the constancy of those effects, and calculating preservation curves similar to Figure 2. This has not been done here, but may be possible.

Various safety analyses show no cause for concern.

Thus, VALIANT can be described as reassuring in numerous respects, even if one cannot be sure that valsartan is not materially inferior to captopril. I conclude that VALIANT results do provide adequate evidence that valsartan would have been superior to placebo, had placebo been present. Therefore, valsartan should have a claim for use in an ACE inhibitor-intolerant population in the setting of a recent myocardial infarction and heart failure or left ventricular dysfunction.

Intolerance to ACE inhibitors probably has nothing to do with properties underlying their benefits. Therefore, it is not necessary to have explicit demonstration that valsartan is effective in a population intolerant of ACE inhibitors.

The sponsor provided categorical denial of inappropriate financial arrangements with investigators as defined in 21CFR54.2(a), (b), and (f). Financial disclosure forms were obtained from more than 99% of investigators. Only the PI indicated significant payments in support of study activities and only one other investigator indicated significant equity interest. The documentation appears to be adequate and there are no concerns about financial disclosure.

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/s/

Norman Stockbridge
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MEDICAL OFFICER

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Minutes of a Meeting between Novartis and the FDA

Date: February 09, 2005

Application: NDA 21-283/S-011
Diovan (valsartan) Tablets

Sponsor: Novartis Pharmaceuticals, Inc.

Subject: Resubmission Strategy following Approvable Letter

FDA Participants

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation I
Norman Stockbridge, M.D., Ph.D., HFD-110, Acting Director, Division of Cardio-Renal Drug Products
Charles Anello, Sc.D., HFD-700, Deputy Director, Office of Biostatistics
Kooros Mahjoob, Ph.D., HFD-710, Acting Director, Division of Biometrics I
Edward Fromm, HFD-110, Chief, Project Management Staff

Novartis

Francis Plat, MD - Executive Director, Cardiovascular CD&MA
William Daley, MD - Executive Director, Cardiovascular CD&MA
Steve Zelenkofske, MD - Director, Cardiovascular CD&MA
Angelo Trapani - Clinical Research Manager, Cardiovascular CD&MA
Tom Chiang, PhD - Director, Biostatistics and Statistical Reporting
Jim Gong, PhD - Associate Director, Biostatistics and Statistical Reporting
Suman Shirodkar, MD, PhD - Director, Cardiovascular Marketing
Math Hukkelhoven, PhD - Global Head, Drug Regulatory Affairs
Adrian Birch - Executive Director, Drug Regulatory Affairs
Nancy Price - Director, Drug Regulatory Affairs
Soraya Madani, FDA Liaison, Drug Regulatory Affairs

Background

NDA 21-283/S-011, submitted on December 17, 2003, contained the results of the VALIANT (VALsartan In Acute myocardial infarction) trial, a randomized, active-controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and signs, symptoms or radiological evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction.

The Division issued an approvable letter on January 13, 2005 for use of valsartan in patients post myocardial infarction who are intolerant to ACE inhibitors. In the letter, the Division asked for additional data to support a claim as a substitute for an ACE inhibitor in this population as well as the effects of captopril or other ACE Inhibitors on secondary endpoints in the trial.

The meeting today is to discuss the sponsor's February 2, 2005 response to the approvable letter and to determine what additional information is needed to support an unrestricted claim in this patient population.

Meeting

Dr. Temple opened the meeting by noting that we believe that based on the non-inferiority margin for the trial, valsartan has an effect in the post-myocardial infarction setting, and that it comes close to preserving 50% of captopril's effect. He said we are still reviewing the firm's February 2, 2005 submission and other analyses to see if valsartan could be used as a substitute for an ACE inhibitor in this patient population.

Novartis noted that they believe that the patient populations in the SAVE, AIRE, and TRACE trials were similar when compared to the VALIANT population. They presented a slide that detailed the results of a composite endpoint (CV Death/MI/CHF) for this comparison and noted the similarity in event rates.

Novartis noted that CV death (mortality) was common in all three trials (SAVE, AIRE, and TRACE) and presented a slide that they believe shows that a meta analysis of the three trials for this endpoint when compared to the VALIANT results show about a 50% preservation of captopril's effect. Dr. Temple noted that using a lower bound of 1.168 to show any effect was not very conservative, but that the lower bound of 1.08 was conservative. We would be prepared to approve valsartan generally (not just in people who cannot use an ACE inhibitor), if we can reliably assure 50% retention of the mortality effect of captopril.

Dr. Temple asked how CV deaths were calculated for the VALIANT trials. The firm replied that they used a Central Committee for assessing these deaths. They further noted that a Central Committee was used for adjudicating all events for the SAVE, AIRE, and TRACE trials.

Dr. Temple asked if the lower bound for the endpoint of CV Death/MI/CHF was known for the SAVE trial alone. Novartis presented a slide that showed that the lower bound was 1.149 and the SAVE study alone gave 1.074 for 50% of the 95% CI lower bound of captopril's effect., Dr. Temple said these data were helpful as they appear to show that using just SAVE alone, 50% of captopril's effect for this endpoint were preserved using a 95%/95% CI. He encouraged the firm to formally submit these arguments to the Division for review.

Dr. Temple asked how close were the results of a composite of the secondary endpoints from VALIANT with respect to SAVE. The firm replied that the lower bound was 1.025, which they believed was close to winning for these endpoints.

Novartis noted that an adjustment for high beta-blocker use in VALIANT gives an even greater preservation of the mortality effect of captopril in the trial. Dr. Temple said this information is helpful and suggested that the firm submit these data and the following arguments to the Division for further review:

1. Describe the evidence that 50% of Captopril's effect is retained. Submit all meta-analyses relating to this argument, both favorable and unfavorable. Certainly the beta-blocker case as noted above would be a strong reference.
2. Submit data showing that for the endpoint of CV Death/MI/CHF, the VALIANT lower bound for this endpoint was very close to the conservative non-inferiority threshold.
3. Provide data on the secondary endpoints of hospitalization for heart failure and new MI that show that they trend in the right direction. If these data are positive, they could be included in the labeling as an expanded claim. Stroke would not be included as it appeared that it trended in the wrong direction. He did note that because of the non-inferiority analyses done to support these data, no p-values would be assigned to both the primary and secondary endpoints in the trial in the labeling. Novartis presented a slide that showed that the percentage of individual component

endpoints in the composite secondary endpoints in VALIANT (valsartan vs. captopril) were consistent.

4. Send in revised labeling and think about the use of figures such as those presented in the slides as a way of conveying information about the primary and secondary endpoints in the trial.

Class 1 vs. Class 2 Resubmission

Novartis said they would send in the abovementioned data and asked if this resubmission could be considered a Class 1 resubmission (2-month goal date). Dr. Temple said he believes that the above analyses still require considerable internal discussion and therefore should be classified as a Class 2 resubmission, although we certainly do not anticipate taking 6 months to complete the review of these data. Novartis argued that the analyses asked for by the Agency are relatively minor analyses and should be classified as a Class 1 resubmission. Dr. Temple disagreed, but said that we would classify the February 2, 2005 submission as a Class 2 resubmission, moving the date earlier.

Minutes Preparation:

Edward Fromm

Concurrence, Chair:

Robert Temple, M.D.

Drafted: ef/2/15/05-2/25/05-3/02/05

Final: NStockbridge-2/25/05
KMahjoob-2/23/05
JHung-2/23/05

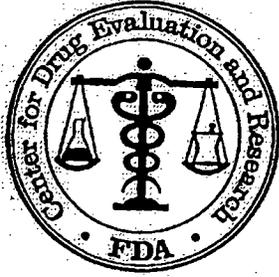
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/s/

Robert Temple
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DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 21-283 Valsartan

Sponsor: Novartis

Submission: SE1-011 (17 December 2003): a request to approve valsartan for use post myocardial infarction.

Review date: 22 April 2005

From: N. Stockbridge, M.D., Ph.D., Acting Director, HFD-110

Distribution: NDA 21-283
HFD-110/Project Manager
HFD-100/Temple

This memo reiterates and expands upon a position taken with the previous memo.

Interpretation of any trial requires some assumptions to conclude that the results are going to apply to a more general population and in less well-controlled clinical practice. Interpretation of a placebo-less trial intended to show the new therapy is not too much worse than some reference therapy requires additional assumptions. In this particular case, to develop a non-inferiority margin, one has to rely not only on historical immutability of the relative risk reduction associated with the reference treatment, one has to rely also upon assumptions that the effects of three ACE inhibitors are the same, despite the observation that the reference agent in the trial was the least effective among those historical trials.

If these assumptions hold, the conclusion that valsartan is superior to placebo is very robust and the conclusion that valsartan is associated with preservation of at least half of the effect of ACE inhibitor is marginal. The very robust nature of the conclusion that valsartan is effective provides substantial protection against the consequences of the underlying assumptions being incorrect. The marginal statistical significance around the preservation of 50% of the effect of captopril protects one scarcely at all from the consequences of fallacious assumptions.

Thus, I believe valsartan is effective, but, despite close point estimates for the effect size, I do not believe that VALIANT provides compelling evidence that valsartan should be considered interchangeable with captopril in the treatment of patients following myocardial infarction.

For these reasons, I support approval of valsartan for this use, but I believe it should be recommended only in patients intolerant of ACE inhibitor.

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/s/

Norman Stockbridge
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MEDICAL OFFICER

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Fromm, Edward J

From: Best, Jeanine A
Sent: Monday, May 02, 2005 9:56 AM
To: Fromm, Edward J; Smith, Christine M
Subject: RE: PI and PPI for Diovan (valsartan) Tablets for Post-Myocardial Infarction, NDA 21-283/S-011

Ed, I have a few suggested edits for the PPI.
Jeanine



VALIANT PPI
50205jab.doc (133)

-----Original Message-----

From: Fromm, Edward J
Sent: Monday, May 02, 2005 9:28 AM
To: Smith, Christine M; Best, Jeanine A
Subject: PI and PPI for Diovan (valsartan) Tablets for Post-Myocardial Infarction, NDA 21-283/S-011

Christine and Jeanine,

I've attached the proposed PI and PPI for Diovan (valsartan) Tablets for Post-Myocardial Infarction, NDA 21-283/S-011. We've essentially reached agreement with the sponsor on the labeling and would like your comments, if any, on the changes.

If you need a formal consult, please let me know, however, we'll need comments back as soon as possible.

The PPI for Diovan was approved last year and the modifications to it have to do with the new post-MI indication.)

Thanks

Ed

<< File: Markup of VALIANT PPI (4-27-05).doc >> << File: Valiant Revised-4-22-05 (2).doc >>

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Fromm, Edward J

From: McLeroy, Lance
Sent: Tuesday, May 03, 2005 2:56 PM
To: Fromm, Edward J
Subject: Diovan

Good afternoon Dr. Fromm.

I just reviewed the revised PI and PPI for Diovan. I only had two small edits on page 7 of the PI and on page 1 of the PPI.



Valiant
VALIANT PPI
vised-4-22-05 (2).d0205 DSRCS DDMAc

Thank you for the consult. Please do not hesitate to email me directly (or through DFS) if there is anything else I can do for you or the review division.

Thank you.

Lance

Lance McLeroy, Pharm.D., M.S.
LT, United States Public Health Service
Regulatory Review Officer
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Work: 301-827-2831
Fax: 301-594-6771

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Memorandum

To: Norman Stockbridge
From: Robert Temple, MD
Date: August 2, 2005
Subject: NDA 21-283/SE1-011 – valsartan post-AMI

There is agreement that VALIANT clearly shows valsartan to have an effect on post infarction outcome (mortality) but some debate as to whether it has been shown to be similar enough to an ACEI to merit an unrestricted claim, as opposed to a recommendation for use only in people who cannot tolerate an ACEI.

A problem in non-inferiority evaluations is that where we are dealing with modest effects of the control (say a 25% reduction vs placebo in event rate), the sample sizes needed to assure us of substantial retention, say 75%, of the control effect, if the drugs are truly equivalent, become enormous. We have therefore accepted as "good enough," even in matters of life and death, assurance of 50% retention (i.e., a 95% CI that excludes a loss greater than this) of the control effect (the value chosen for thrombolytics). This is a difficult issue; after all, the reason you cannot do a placebo-controlled trial in these cases is the perceived value of the active control. Plainly, you do not want to lose too much of that effect. On the other hand, we regularly accept placebo-controlled trials, if they can be done (consider post-infarction beta-blockers, ACEI's for post-infarction use, studies of iib/iiia inhibitors), even without any direct comparison to a known effective agent, despite possible differences between one treatment and another. (The 95% lower bound of the CI for SAVE, e.g, is a considerably lower than that in AIRE and TRACE but that has not troubled us). We do this, I believe, because we do pay some attention to point estimates, because we take into account expectations (priors) for pharmacologically similar drugs, and because smaller differences simply cannot be ruled out with studies that can be conducted.

Given past practices and our prior beliefs in this setting, I believe the available data on valsartan from the VALIANT trial support a conclusion of non-inferiority of valsartan to ACEIs, notably captopril, and unrestricted

labeling for valsartan for use following an acute myocardial infarction. Let me explain the reasons for this conclusion

1. Non-inferiority

According to Dr. Hung, the 90-97.5 (one-sided) approach (similar to the 90-95% approach CBER did with thrombolytics; use the 90% lower bound of the C.I. to establish the NI margin, then look at the 95% CI for the new drug vs active control comparison; we used a 97.5% upper bound instead of 95% because these were multiple comparisons – the trial also had a captopril plus valsartan vs captopril comparison) indicates that valsartan retains about 50% of the effect of the 3 ACE inhibitors (pooled results) on mortality or of 50% of the effect of captopril itself, based on SAVE, on the combined endpoint of CV mortality, CHF hospitalization, and recurrent AMI, particularly if beta blocker use is also considered in the NI analysis. I will not address the details of those analyses here except to note that the mortality comparison depends on pooling the results of SAVE, AIRE, and TRACE to obtain a reasonable lower bound for the effect of the ACEI's. As I have suggested, an alternative would be to use the point estimate for SAVE and allow the results of AIRE and TRACE with ramapril and tramdolapril, 2 drugs with pharmacologic effects very similar to captopril, to narrow the confidence interval for the SAVE results. This is not a "standard" approach, but seems an appropriate use of a "prior" (all 3 drugs are ACEI's and all 3 were successful). In fact, when this was done by Dr. Hung, we get results quite similar to the pooled analysis, which I find reassuring. The 50% retention on the composite endpoint is based entirely on SAVE, and thus only captopril, the comparator in VALIANT.

2. Comparison with placebo control

Although it is easy to forget this when we talk about studies trial results do not show that a drug had an effect equal to the point estimate, and this is true for both placebo controlled and NI studies. SAVE did not show an actual 19% decrease in mortality. It showed an effect greater than zero with a 95% C.I. lower bound of 3%. So we're 95% sure the effect was at least 3%. We have no good basis at all for comparing the effect of captopril, trandolapril and ramapril, knowing only that each is better than placebo. The point estimates (19% for SAVE, 27% for AIRE, and 22% for TRACE) can't really be used for comparisons because results are so population-dependent. What we are pretty sure of is that they are effective. Under the present circumstances, in contrast, we can be quite sure

August 2, 2005

that valsartan has an effect in the same range as captopril. The point estimate of the comparison is actual equivalence and a large difference (more than about 50%) has been ruled out. We therefore know almost as much about valsartan's effect vs placebo as we would if valsartan had been studied in a placebo controlled trial (not quite as much because there is still the constancy assumption), and rather more about the comparative effect of valsartan and ACEI's than we do about the comparative effects of the ACE inhibitors.

I therefore conclude that we can be confident enough of valsartan's post-infarction effectiveness to approve it without reservation and need not limit its use to people who cannot tolerate an ACEI.

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/s/

Robert Temple
8/3/05 01:42:09 PM
MEDICAL OFFICER

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**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
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Transmitted to FAX Number: (973) 781-3590

Attention: Mr. Adrian Birch

Company Name: Novartis Pharmaceuticals

Phone: (862) 778-3589

Subject: Approval Letter & Labeling
for NDA 21-283/S-011

Date: August 3, 2005

Pages including this sheet: 21

From: Edward Fromm

Phone: 301-594-5328

Fax: 301-594-5494

RHPM NDA Efficacy and Labeling Supplement Approval Review
August 3, 2005

Diovan (valsartan) Tablets for the Treatment of Patients with Post-Myocardial Infarction

NDA 21-283/SE1-011

Applicant: Novartis Pharmaceuticals Co.

Classification: SE1 (new indication)

Review Classification: Standard

Indication: Post-Myocardial Infarction-In clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction, Diovan is indicated to reduce cardiovascular mortality.

Date of Application: December 17, 2003

Date of AE Letter: January 13, 2005

Date FPL Submitted: April 28, 2005 (Package Insert)

Date FPL Received: April 29, 2005 (Package Insert)

Date FPL Submitted: June 29, 2005 (Patient Package Insert)

Date FPL Received: June 30, 2005 (Patient Package Insert)

User Fee Goal Date: August 4, 2005

Background

This efficacy supplement, submitted on December 17, 2003, contains the results of the VALIANT (VALsartan In Acute myocardial iNfarction) trial, a randomized, controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and signs, symptoms or radiologic evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction.

In response to a request from the Division during a teleconference on September 9, 2004, Novartis submitted on October 1, 2004, additional data to support their claim that valsartan is an acceptable alternative to an ACE inhibitor in patients who have experienced a myocardial infarction (MI). The Division considered this submission a major amendment with the review clock being extended by 3 months. Consequently, the new goal date for the application was extended to January 17, 2005.

The Division issued an approvable letter on January 13, 2005 for use of valsartan in patients post-myocardial infarction who are intolerant to ACE inhibitors. In the letter, the Division asked for additional data to support a claim as a substitute for an ACE inhibitor in this population as well as the effects of captopril or other ACE Inhibitors on secondary endpoints in the trial. Novartis met with the Agency on February 9, 2005, to present new analyses of the VALIANT data and argued that valsartan preserves at least 50% of captopril's effect in the post-myocardial population. Dr. Temple thought the sponsor's arguments were plausible, but asked for the following additional information:

1. Describe the evidence that 50% of Captopril's effect is retained. Submit all meta-analyses relating to this argument, both favorable and unfavorable. Certainly the beta-blocker case as noted above would be a strong reference.
2. Submit data showing that for the endpoint of CV Death/MI/CHF, the VALIANT lower bound for this endpoint was very close to the conservative non-inferiority threshold.
3. Provide data on the secondary endpoints of hospitalization for heart failure and new MI that show that they trend in the right direction. If these data are positive, they could be included in the labeling as an expanded claim. Stroke would not be included as it appeared that it trended in the wrong direction. He did note that because of the non-inferiority analyses done to support these data, no p-values would be assigned to both the primary and secondary endpoints in the trial in the labeling. Novartis presented a slide that showed that the percentage of individual component endpoints in the composite secondary endpoints in VALIANT (valsartan vs. captopril) were consistent.
4. Send in revised labeling and think about the use of figures such as those presented in the slides as a way of conveying information about the primary and secondary endpoints in the trial.

The Agency did agree at this meeting that a submission dated February 2, 2005, that contained additional reanalyses of the VALIANT data would be classified as a Class 2 resubmission for the supplement. Consequently, the PDUFA goal date for the application was extended 6 months to August 4, 2005.

Novartis submitted the data requested the data requested in the February 9th meeting on March 3, 2005. After internal discussion of these new data, the Agency agreed that the indication for post-myocardial infarction would not be restricted to patients who are intolerant to ACE inhibitors (Note: Dr. Stockbridge in his memo dated April 22, 2005 disagreed with this conclusion and thought the restriction to patients with ACE inhibitors should remain. In a memo dated August 3, 2005, Dr. Temple explained his reasoning as to why there should not be a restriction to patients who are intolerant to ACE inhibitors).

The Agency also removed the restriction of patients who are intolerant of angiotensin converting enzyme inhibitors was removed from the Heart Failure subsection of the **INDICATIONS AND USAGE** section of the labeling. This was done on the basis of the previous subset finding in the Val-HeFT trial as well as new information from the CHARM program which involved the angiotensin II blocker candesartan.

After several e-mail exchanges with Novartis regarding the labeling, the sponsor was informed that they could send in final printed labeling (FPL). Electronic FPL was submitted by Novartis on April 28, 2005 with the following revisions:

1. **CLINICAL PHARMACOLOGY**, _____

2. **CLINICAL PHARMACOLOGY**, *Pharmacodynamics and Clinical Effects*. a new subsection has

3. Under **INDICATIONS AND USAGE**, **Heart Failure**, _____

4. Under **INDICATIONS AND USAGE**, a new subsection has been added entitled "**Post-Myocardial Infarction**" that reads as follows:

In clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction, Diovan is indicated to reduce cardiovascular mortality. (See **CLINICAL PHARMACOLOGY**, Pharmacodynamics and Clinical Effects, Post Myocardial Infarction).

5. Under **WARNINGS, Hypotension**, the subheading **Hypotension in Heart Failure Patients** has been deleted and this paragraph revised as follows:

Caution should be observed when initiating therapy in patients with heart failure or post-myocardial infarction patients. Patients with heart failure or post-myocardial infarction patients 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 in heart failure patients, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), hypotension in post-myocardial infarction patients led to permanent discontinuation of therapy in 1.4% of valsartan-treated patients and 0.8% of captopril-treated patients.

6. Under **PRECAUTIONS, Impaired Renal Function**, the following statement has been added to the 4TH paragraph of this subsection, "In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), discontinuations due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients." Note also the previous subheadings of _____ have been deleted so that only the subheading "**Impaired Renal Function**" remains.

7. Under **PRECAUTIONS**, the 5th paragraph with the subheading _____ has been deleted.

8. Under **PRECAUTIONS, Geriatric Use**, the 2nd paragraph has been revised 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. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), 53% (2,596) of the 4,909 patients treated with valsartan and 51% (2,515) of the 4,885 patients treated with valsartan + captopril were 65 years of age or older. There were no notable differences in efficacy of safety between older and younger patients in either trial.

9. Under **ADVERSE REACTIONS**, a new **Post-Myocardial Infarction** subsection has been added that details the adverse event profile for the VALIANT trial.

10. Under **ADVERSE REACTIONS, Post-Marketing Experience**, the statement "Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers" has been added.

11. Under **ADVERSE REACTIONS, Clinical Laboratory Test Findings, Creatinine**, the statement "in post-myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients and 3.4% of captopril-treated patients" has been added.

12. Under **DOSAGE AND ADMINISTRATION, Heart Failure**, _____

13. Under **DOSAGE AND ADMINISTRATION**, a new **Post-Myocardial Infarction** subsection has been added that reads as follows:

Diovan may be initiated as early as 12 hours after a myocardial infarction. The recommended starting dose of Diovan is 20 mg twice daily. Patients may be uptitrated within 7 days to 40 mg twice daily, with subsequent titrations to a target maintenance dose of 160 mg twice daily, as tolerated by the patient. If symptomatic hypotension or renal dysfunction occurs, consideration should be given to a dosage reduction. Diovan may be given with other standard post-myocardial infarction treatment, including thrombolytics, aspirin, beta blockers, and statins.

14. Under **HOW SUPPLIED**, the second sentence has been changed to read as follows:

40 mg tablets are scored on one side and ovaloid with bevelled edges. 80 mg, 160 mg, and 320 mg tablets are unscored and almond-shaped with bevelled edges.

There are also changes in the bottle and blister identification numbers in the table listing the characteristics of the different tablet strengths in this section.

Comments/Recommendations: The labeling revisions above were those noted when compared with the last approved labeling supplement (S-001, Approved August 14, 2002). The final PPI (Patient Package Insert) for Diovan was submitted June 29, 2005 and has been revised to reflect the new Post-Myocardial Infarction indication. However, during the routing process, Dr. Hung objected to certain language in the fourth paragraph of the **CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Post-Myocardial Infarction** subsection. This paragraph was rewritten and agreed to by the sponsor in an e-mail exchange with the Agency dated July 14, 2005. Because the revisions to the paragraph are more than minor editorial changes, the approval letter will ask for final printed labeling to be submitted.

I will draft an approval letter with agreed-upon labeling text (including PPI) for Dr. Temple's signature.

Edward Fromm
Regulatory Health Project Manager

dr-ef-8-03-05

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RHPM NDA Efficacy Supplement Overview
January 3, 2005

Diovan (valsartan) Tablets for the Treatment of Patients with Post-Myocardial Infarction

NDA 21-283/SE1-011

Sponsor: Novartis Pharmaceuticals, Inc.

Classification: SE1 (new indication)

Review Classification: Standard (10 month review)

Indication: Treatment of patients with post-myocardial infarction

Date of Application: December 17, 2003

User Fee Goal Dates: October 17, 2004 (extended to January 17, 2005)

Background

This efficacy supplement, submitted on December 17, 2003, contains the results of the VALIANT (VALsartan In Acute myocardial iNfarction) trial, a randomized, controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and signs, symptoms or radiologic evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction. Novartis believes that valsartan in the overall VALIANT study population, demonstrated equivalent efficacy to captopril. They also believe that valsartan was shown to be efficacious and safe in post-myocardial infarction patients who did not receive ACE inhibitor therapy.

In response to a request from the Division during a teleconference on September 9, 2004, Novartis submitted on October 1, 2004, additional data to support their claim that valsartan is an acceptable alternative to an ACE inhibitor in patients who have experienced a myocardial infarction (MI). The Division considered this submission a major amendment with the review clock being extended by 3 months. The new goal date for the application is January 17, 2005.

In response to a request from the Division on October 9, 2004, Novartis submitted additional information regarding the use of beta-blockers in the VALIANT study. A meeting was held on December 17, 2004 with the applicant to discuss this submission as well as the overall progress of the trial. At this meeting, Novartis presented arguments that valsartan retains a much higher mortality effect of captopril than that concluded by the Agency. They agreed to submit the following items to support these arguments:

1. Multiplicity adjustment for the control (captopril) is excessive
2. A per-protocol analysis of the data give a higher retention of mortality effect of captopril
3. An adjustment for the high beta-blocker use in the trial results in a higher preservation of the captopril effect.
4. CV secondary endpoints in the trial all point in the right direction and are supportive of the non-inferiority margin chosen by the firm.
5. Raw (source) data from the SAVE trial.
6. Other data that can argue for the robustness of the trial results.

Novartis submitted the source data for the SAVE trial to the Division on December 22, 2004 and the other agreed-upon data on December 29, 2004. At a meeting on January 12, 2005, the Agency agreed that the data for valsartan support a higher preservation of the mortality effect of captopril, although we are uncertain whether this evidence is conclusive enough to support the use of valsartan as a substitute for an ACE inhibitor in this patient population. It was agreed that the applicant would submit data on the secondary endpoints in the other referenced trials (AIRE, SAVE, & TRACE) to show their effect on captopril. The Division suggested that the firm make arguments about the clinical meaningfulness of the VALIANT results in support of valsartan as a substitute directly to Dr. Temple at a future meeting.

Clinical investigations of Diovan for the treatment of post myocardial infarction in the United States were conducted under IND 40,783.

Meetings

End-of Phase 2: April 29, 1996

Guidance: July 14, 1998, December 17, 2004

Pre-NDA: September 16, 2003

Review

Medical

Division Director: Norman Stockbridge, M.D., Ph.D.

Conclusion: Approvable

Dr. Stockbridge believes that the VALIANT study results support the use of valsartan in patients that who are intolerant to ACE inhibitors but not as a substitute (alternative) to an ACE inhibitor. In text for the approvable letter for this supplement, he notes that the sponsor "will need to address why these results support use in a population able to take ACE inhibitors. Our proposed restriction to this population is the result of concerns engendered by the reliance on multiple drugs to set the non-inferiority margin, the comparison with Diovan being made with what appears to be the least effective of the ACE inhibitors, and the long lag between the SAVE, AIRE, and TRACE studies and VALIANT. These concerns undermine our confidence that VALIANT shows Diovan to be interchangeable with captopril, but does not completely erode our confidence that Diovan is effective. We believe that ACE intolerance is unlikely to be related to mechanisms by which ACE inhibitors and Diovan exert beneficial effects, so we do not believe it is necessary to study this population directly.

The proposed presentation of results on secondary end points does not factor in what is known about effects of captopril or the other ACE inhibitors on them. Without this context, it is not possible to interpret the nominal hazard ratios observed in VALIANT."

Medical/Statistical: Shari Targum, M.D.

James Hung, Ph.D.

Conclusion: Not Approvable, Dr. Targum states in her clinical review dated July 15, 2004 that "since VALIANT was an active-controlled study, without a

placebo control, the issues of non-inferiority and effectiveness of valsartan depend on analysis of margins and choice of historical study as a basis for captopril (and placebo) effect. She notes that "different analyses (of the data) have yielded different outcomes" and that she is uncertain on which analysis to choose. Therefore Dr. Targum recommends "against approval, arguing the weight of evidence does not support approval."

In his statistical addendum dated??? Dr. Hung noted that "the beneficial effects of ACE inhibitors and beta blockers are independent, additive, and consistent across all three historical trials (SAVE, AIRE, TRACE)." However, the "key clinical question is whether captopril's mortality effect is smaller in VALIANT than in the historical trials." He notes that the constancy assumption the sponsor uses could allow for the use of the worst limit of the 90% two-sided confidence interval and with this approach, valsartan retains at least 42%-53% of the mortality benefit of captopril. Dr. Hung says further, "if the constancy assumption is in doubt, based on the traditional approach using the worst limit of 95% two-sided confidence interval to estimate the captopril effect, VALIANT can support that valsartan retains at least 36%-44% of the mortality benefit of captopril."

Labeling: None

Biopharmaceutics

Reviewer: Nhi Beasley, PharmD.

Labeling: None

Conclusion: Biowaiver should be granted for the 40 mg ovaloid scored tablet. The current dissolution specification and methodology listed below should apply to the new tablet:

Medium: p.H. 6.8 (0.067 M phosphate buffer)

Apparatus: USP II (paddle)

Volume (mL): 1000 mL

Speed: 50 rpm

Specification: _____

Chemistry

Reviewer: Stuart Zimmerman, Ph.D.

Labeling: None

CGMP Inspections: Not applicable

Methods Validation: Not applicable

Environmental Assessment: FONSI granted

Conclusion: Approvable

Pharmacology

Reviewer: Anthony Proakis, Ph.D.

Labeling: None

Conclusion: Dr. Proakis noted that these supplemental applications for valsartan "contain no new preclinical pharmacology/toxicology study reports"

requiring review. Likewise, the sponsor's proposed changes of the product labeling are limited to the clinical studies and contain no changes from the previously approved summaries of the non-clinical studies. Therefore, a pharmacology/toxicology review for this NDA supplement is not necessary."

- Statistics (preclin): Not needed
- Safety Update: No additional safety data since original submission dated December 17, 2003.
- Patent info: Included in package
- Pediatric info: Waived
- DSI: Acceptable, "The inspections revealed nothing that would be expected to impact the validity of the data submitted for the three sites inspected."
- Debarment Certification: Included in package
- Exclusivity Summary: Will be addressed at time of approval
- Financial Disclosure: The sponsor denies having any inappropriate financial arrangements (see Dr. Targum's Medical Review).
- OPDRA Tradename Review: Not needed, the firm did not change the trade or generic name for this new indication.
- Comments: I will draft an approvable letter without labeling for Dr. Stockbridge's signature.

Edward J. Fromm

dr-ef-1-13-05

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NDA 21-283/S-011

There have been no safety updates since the safety update of March 30, 2004.

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§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling