1. (NDA 20-665/S-016)-Under **DESCRIPTION**, 5th sentence, please add after iron oxides, in parentheses, the individual color components (yellow, black, brown, and/or red).
2. (NDA 21-283/S-001)-Under **DESCRIPTION**, 5th sentence, please insert the word "brown" after the word "black" in the parentheses (yellow, black, and/or red).

I will draft an approval letter with labeling for these supplements for Dr. Temple's signature. Per Dr. Throckmorton's instructions, the Pediatric Rule Requirements for this indication will be deferred until September 30, 2007 (5 years).

/S/

Edward J. Fromm
Regulatory Health Project Manager

dr-ef-8-14-02

RHPM NDA Efficacy Supplement Overview (Updated)
July 17, 2002

Diovan (valsartan) for CHF

NDA 20-665/SE1-016 (capsules)
NDA 21-283/SE1-001 (tablets)

Sponsor: Novartis Pharmaceuticals, Inc.

Classification: SE1 (new indication)

Review Classification: Priority (6 month review)

Indication: Treatment of Heart Failure

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

User Fee Goal Date: July 23, 2002

Background

An approvable letter was issued on October 24, 2001 for valsartan for CHF for both NDA 20-665/S-016 and NDA 21-283/S-001. The letter stated that before approval could be granted a second study in patients in who cannot tolerate an ace inhibitor would be needed to confirm the striking positive morbidity and mortality results achieved in the "no ACEI" subset of the Val-HeFT trial. Alternatively, the sponsor could conduct an "examination of the Val-HeFT exercise substudy and the many secondary endpoints in the no-ACEI patients in Val-HeFT (that) could strengthen the subset findings further."

Novartis met with the Agency on December 13, 2001, and agreed at the meeting to submit the following:

- Retrospective analyses of how valsartan plus different doses (i.e., low & high) of ACE inhibitors affected morbidity and mortality endpoints.
- Retrospective analyses of the ETT (exercise tolerance test) sub-studies from trials 106 and 107 showing the effect of different doses of ACE inhibitors on morbidity and mortality endpoints.
- Any other analyses that would support approval of valsartan in the treatment of heart failure.

Dr. Temple noted that these analyses, when submitted, would be considered the firm's formal response to the approvable letter and the Agency would classify them as a type II resubmission (6 month PDUFA review clock).

Novartis on January 22, 2002 (our receipt date, January 23, 2002) submitted the retrospective analyses requested at the December 13, 2002 meeting. Consequently, the PDUFA action date became July 23, 2002. Revised draft labeling for both supplements was sent by the firm on February 12, 2002.

At an internal meeting on July 3, 2002, Dr. Temple and members of the Division met to discuss what action to take on the applications by the July 23, 2002 goal date. Dr. Throckmorton and other members of the Division stated that valsartan's effect in the no ACE-Val-Heft subset was a strong

signal of efficacy but believed that it should be replicated with another study, such an ETT. Although not present at the meeting, Dr. Stockbridge believes the overall data support the use of the drug as a substitute for an ACE inhibitor in heart failure and no further studies were necessary. Dr. Temple said he thought the no ACE inhibitor results were very persuasive but there was not enough evidence to indicate valsartan as substitute for an ACE inhibitor in the treatment of heart failure. Instead, he proposed that valsartan be indicated for patients that are intolerant to ACE inhibitors because there were 300 hundred or so patients in the no ACE subset compared with data on thousands of patients on ACE inhibitors that clearly show that it is effective in the treatment of heart failure.

At a telecon between Novartis and the Agency on July 16, 2002, Dr. Temple said that we would issue an approvable letter with marked-up draft labeling by the July 23, 2002 goal date. The letter will say that valsartan is approvable for the treatment of heart failure in patients who are intolerant to ACE inhibitors. The marked-up draft labeling that will accompany the letter will focus on the no ACE subset that drove the overall positive result for the Val-Heft trial for hospitalizations, particularly cardiovascular hospitalizations. We will show endpoints of the subset, but not p values. In addition, the apparent negative interaction of valsartan when given to patients that are taking both an ACE inhibitor and beta blocker will be described in the labeling.

An approvable letter with marked-up draft labeling will be drafted for Dr. Temple's signature.

Edward J. Fromm
Regulatory Health Project Manager

dr-ef-7-17-02

Fromm, Edward J

From: Cropp, Cheryl
ent: Wednesday, July 31, 2002 11:16 AM
To: Fromm, Edward J
Subject: RE: Sponsor Meetings on 7/26

Ed,

I just completed my review of the Diovan labels. I don't have any comments.

Thanks,
Cheryl

-----Original Message-----
From: Fromm, Edward J
Sent: Wednesday, July 31, 2002 8:40 AM
To: Cropp, Cheryl
Subject: RE: Sponsor Meetings on 7/26

Cheryl,

Diovan (valsartan) for Heart Failure was issued an approvable letter on July 23, 2002. The firm has submitted final printed labeling already and Dr. Temple and Throckmorton have said it is acceptable. So if you have any comments I would need them as soon as possible. I will send you their FPL. Please note that there are two sets of labeling, one for NDA 21-283/S-001 (Tablets) & one for NDA 20-665/S-016 (Capsules). It is my understanding that the company plans to not market the capsules in the not too distant future.

Thanks,

Ed

<< File: N21283-S001PInovartis comments29JUL02.DOC >>
<< File: N20665-S016PI novartis comments 29JUL02.DOC >>
<< File: 7 24 02 draft labeling FDA.doc >>

-----Original Message-----
From: Cropp, Cheryl
Sent: Wednesday, July 31, 2002 8:24 AM
To: Fromm, Edward J
Subject: Sponsor Meetings on 7/26

Hi Ed,

Could you provide me with a quick summary of last Friday's t cons for Diovan since I was unable to participate?

Also, I'm working on the Diovan label now. When is it due?

Thanks,

Cheryl

APPEARS THIS WAY
ON ORIGINAL

RHPM Filing Review

Application:	NDA 20-665/SE1-016 Diovan (valsartan) Capsules for CHF 80 and 160 mg
Applicant:	Novartis Pharmaceuticals
Application Date:	April 27, 2001
Receipt Date:	April 27, 2001
User Fee Goal Date:	October 27, 2001 (Priority Review)

Background

Novartis has submitted this efficacy supplement for valsartan for CHF. Valsartan, an angiotensin II receptor blocker, is currently indicated for the treatment of hypertension. Studies for valsartan for CHF were conducted under IND [redacted]

The application for efficacy and safety is supported principally by 4 placebo (#'s 103, 104, 106 and 107-Val-HeFT) and 1 active controlled studies. Novartis claims that valsartan significantly reduced by 13.2% the primary endpoint of time to first morbid event, defined as all-cause mortality, heart failure hospitalization, sudden death with resuscitation, and need for intravenous vasodilator or inotropic therapy when compared to placebo. They also claimed that valartan lessened the time to first heart failure hospitalization (compared to placebo) and exerted significant beneficial effects on a variety of symptomatic endpoints.

The company requested a priority review for this supplement because they believe that Diovan demonstrated a benefit versus placebo in patients treated with existing therapies for heart failure. Dr. Lipicky has decided that the application qualifies for a priority review because the drug could be of benefit in patients that have tried all other CHF therapies.

Meetings

Telecon: July 7, 1994
End-of Phase 2: April 29, 1996

Reviewers:

Chemistry:	Stuart Zimmerman, Ph.D.
Biopharm:	Nhi Nguyen, Pharm.D.
Pharmacology:	Anthony Proakis, Ph.D.
Statistics:	James Hung, Ph.D.
Medical:	Shari Targum, M.D

Review

This supplemental NDA was submitted in paper with the CRF's and CRT's being available electronically (through the Electronic Document Room-EDR).

The index to the supplement is adequate and the application overall appears to be well organized.

The company has requested a waiver for conducting pediatric studies for this indication pursuant to the Pediatric Rule.

The company has submitted a Debarment Certification and Financial Interests and Arrangements of Clinical Investigators Certification.

Deficiencies

40 mg strength

Novartis intends to no longer market the capsule formulation of valsartan and submitted, on August 8, 2000, a separate NDA (21-283) to support 80, 160, and 320 mg tablet strengths of the product. Because of this, they originally planned to submit this CHF supplement to the "tablet" NDA when it was approved this summer. Novartis, however, decided that action could undermine their case for a priority review and so decided to supplement the current "capsule" NDA now with the CHF indication.

The company submitted the application for valsartan capsules for CHF, 80 and 160 mg, but also included CMC and bioequivalence data to support a 40 mg tablet. Studies for the CHF indication were conducted using 40, 80, and 160 mg capsules. The 40 mg strength is not currently in the labeling for hypertension, but is proposed to be the starting dose for the new CHF indication. Unfortunately, because of CDER's bundling policy, the 40 mg "tablet" data cannot be submitted to a "capsule" NDA. Novartis was informed that the 40 mg tablet could not be submitted to the capsule NDA and was advised to amend the current submission so that all references to the 40 mg tablet were deleted. The 40 mg tablet data could be eventually submitted to the tablet NDA once it was approved and the current "capsule" submission could be cross referenced for the CHF clinical data.

Novartis, in a submission dated May 7, 2001, amended the supplement by deleting all references (e.g., to the labeling) for the 40 mg tablet. They will submit the CMC data for the 40 mg tablet to the tablet NDA (21-283) once it is approved. Additional CMC data will be needed for the approval of a 40 mg capsule, if the company decides to pursue this option. It is possible, that the clinical review of the supplement may find that the 40 mg strength is not necessary in either the capsule or tablet form.

Secondary Analyses

Novartis notified the Division, on May 15th, 2002, that they discovered a coding error that may have affected the accuracy of certain tables and listings relevant to secondary endpoints and the handling of subjects who discontinued prematurely. The company emphasized that the error did not change the validity or integrity of the primary efficacy variables and associated conclusions.

On May 29, 2001, Novartis sent in 27 revised volumes and electronic data to reflect the modifications to the tables and listings that were affected.

Recommendation

Provided that the reviewers have not identified reasons for refusing to file, I recommend that the application be filed.

/S/

Edward Fromm
Regulatory Health Project Manager

RHPM NDA Efficacy Supplement Overview
October 15, 2001

Diovan (valsartan) for CHF

NDA 20-665/SE1-016 (capsules)
NDA 21-283/SE1-001 (tablets)

Sponsor: Novartis Pharmaceuticals, Inc.

Classification: SE1 (new indication)

Review Classification: Priority (6 month review)

Indication: Treatment of Heart Failure

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

User Fee Goal Dates: October 27, 2001 (20-665/S-016)
January 23, 2002 (21-283/S-001)

Background

Novartis has submitted these efficacy supplements for valsartan for CHF. Valsartan, an angiotensin II receptor blocker, is currently indicated for the treatment of hypertension. Studies for valsartan for CHF were conducted under IND [redacted]

The application for efficacy and safety is supported principally by 4 placebo (#'s 103, 104, 106 and 107-Val-HeFT) and 1 active controlled studies. Novartis claims that valsartan significantly reduced by 13.2% the primary endpoint of time to first morbid event, defined as all-cause mortality, heart failure hospitalization, sudden death with resuscitation, and need for intravenous vasodilator or inotropic therapy when compared to placebo. They also claimed that valartan lessened the time to first heart failure hospitalization (compared to placebo) and exerted significant beneficial effects on a variety of symptomatic endpoints.

The company requested a priority review for these supplements because they believe that Diovan demonstrated a benefit versus placebo in patients treated with existing therapies for heart failure. Dr. Lipicky granted a priority review for these supplements because the drug could be of benefit in patients that have tried all other CHF therapies.

Novartis intends to no longer market the capsule formulation of valsartan and submitted, on August 8, 2000, a separate NDA (21-283) to support 80, 160, and 320 mg tablet strengths of the product. Because of this, they originally planned to submit this CHF supplement to the "tablet" NDA when it was approved this summer. Novartis, however, decided that action could undermine their case for a priority review and so decided to supplement the current "capsule" NDA with the CHF indication.

The company submitted the application for valsartan capsules (on April 27, 2001) for CHF, 80 and 160 mg, but also included CMC and bioequivalence data to support a 40 mg tablet. Studies for the CHF indication were conducted using 40, 80, and 160 mg capsules. The 40 mg strength is not

currently in the labeling for hypertension, but is proposed to be the starting dose for the new CHF indication. Unfortunately, because of CDER's bundling policy, the 40 mg "tablet" data could not be submitted to the "capsule" NDA. Novartis was informed that the 40 mg tablet data could not be submitted to this NDA and therefore agreed to remove this data from the "capsule" NDA and submit this data to the "tablet" NDA once it was approved. The "tablet" NDA, NDA 21-283, was approved on July 18, 2001. Subsequently, the firm submitted a supplement (S-001, on July 23, 2001) to this NDA that included bioequivalence and CMC data to support a 40 mg strength of the tablet and cross-referenced the CHF clinical data from the "capsule" submission. Since the additional data submitted were relatively minor, the Division informed the firm that barring any unforeseen circumstances, an action would be taken on both supplements by the October 27, 2001 goal date for 20-665/S-016.

These supplements were the subject of an October 11, 2001 meeting of the Cardio-Renal Advisory Committee Meeting. The Committee deadlocked by a vote of 4 to 4 on whether to approve valsartan for the treatment of chronic heart failure. Complicating the decision were subgroup analyses that seemed to show a small positive effect on morbidity for a patient taking a ACE inhibitor but a small negative effect on mortality at the same time. Moreover, patients taking a Beta-Blocker seemed to show a small, negative mortality effect; this effect appeared to be magnified if combined with an ACE inhibitor.

Meetings

Telecon: July 7, 1994
End-of Phase 2: April 29, 1996

Review

Medical

Division Director:	Raymond Lipicky, M.D
Conclusion:	Not Approvable, see Dr. Lipicky's October 15, 2001 Division Director's Memo.
Secondary Medical:	Norman Stockbridge, M.D., Ph.D.
Conclusion:	Approvable
Labeling:	See Dr. Stockbridge's October 15, 2001 review for suggested changes to the **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, WARNINGS,** and **HOW SUPPLIED** sections of the labeling.
Medical/Statistical:	Shari Targum, M.D Abraham Karkowsky, M.D., Ph.D. (Study 110) James Hung, Ph.D. (Statistical review of the Val-heft study, study 107)
Labeling:	None
Conclusion:	Dr. Targum said it appears that valsartan has a positive effect in prolonging the time to first morbid event, especially CHF hospitalizations. She notes that "subgroup analysis shows greater valsartan benefit (mortality and morbidity) in the subgroups not on background ACE inhibitor or beta blocker, versus those patients on background ACE inhibitors/beta blockers (albeit with small numbers of patients not on background ACE inhibitors)." Interestingly, it appears

that valsartan's effect on CHF was less favorable in the US population as compared to the non-US populations in which the drug was studied.

Dr. Targum noted that the Val-heft study demonstrated no survival benefit with valsartan.

Biopharmaceutics
Reviewer: Nhi Nguyen, PharmD.
Labeling: None
Conclusion: approvable; Dr. Nguyen recommended that a bioequivalence waiver be granted for the 40 mg tablet. The 40 mg tablet should have similar specifications as for the other strengths of the tablet:

Medium: 1000 ml of 0.067 M phosphate buffer, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q=[redacted]% in 30 minutes

Chemistry
Reviewer: Stuart Zimmerman, Ph.D.
Labeling: For 20-665/S-016, Dr. Zimmerman suggested that the phrase "[See USP controlled room temperature]" be added to the **HOW SUPPLIED** section of the labeling.

Dr. Zimmerman noted that the following expiration dating be listed for the 40 mg drug product tablet:
a. 18 months for blister packaging and physician samples
b. 24 months for [redacted] bottle trade packages

CGMP Inspections: Acceptable, October 11, 2001.
Methods Validation: Pending
Environmental Assessment: FONSI granted for both supplements
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: Not needed, see Dr. Stockbridge's Secondary Medical Review

Patent info: Included in package

Pediatric info: Deferral, see note in action package

DSI: Acceptable, "No major deficiencies were noted in the four sites inspected that could compromise the integrity of the data. Thus, the data reviewed is acceptable."

Debarment Certification: Included in package

Exclusivity Summary: Included in package

Financial Disclosure: The sponsor denies having any inappropriate financial arrangements (see Dr. Stockbridge's Secondary Medical Review).

OPDRA Tradename Review: Not needed, the firm did not change the trade or generic name for this new indication.

Comments: Per Dr. Lipicky's instructions, an approvable and not-approvable letter will be drafted for Dr. Temple's signature.

Edward J. Fromm

dr-ef-10-15-01

30 pages redacted from this section of the approval package consisted of draft labeling

Minutes of a Telecon between Novartis and the FDA

Date: July 16, 2002

Application: NDA's 20-665/SE1-016 & 21-283/SE1-001
Diovan (valsartan) Capsules and Tablets

Indication: Treatment of patients with CHF (Congestive Heart Failure)

Applicant: Novartis Pharmaceuticals Corporation

Subject: Action Letter

FDA participants

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research
Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
Shari Targum, M.D., HFD-110, Medical Officer
Ms. Natalia Morgenstern, HFD-110, Chief, Project Management Staff
Mr. Edward Fromm, HFD-110, Regulatory Health Project Manager

Novartis

Jay Cohn, M.D., Val-HeFT Study Chairman
Malcolm MacNab, M.D., Ph.D., Vice President, Cardiovascular Clinical Research
Robert Glazer, M.D., Director, Heart Failure Team Leader
Tom Chiang, Ph.D., Director, Biostatistics
Flemming Ornskov, M.D., Vice-President, Cardiovascular Marketing
Mathias Hukkelhoven, Ph.D., Senior Vice-President, Drug Regulatory Affairs
Mr. Adrian Birch, Executive Director, Drug Regulatory Affairs
Ms. Nancy Price, Associate Director, Drug Regulatory Affairs

Background

An approvable letter was issued on October 24, 2001 for valsartan for CHF for both NDA 20-665/S-016 and NDA 21-283/S-001. The letter stated that before approval could be granted a second study in patients in who cannot tolerate an ACE inhibitor would be needed to confirm the striking positive morbidity and mortality results achieved in the "no ACEI" subset of the Val-HeFT trial. Alternatively, the letter notes that an "examination of the Val-HeFT exercise substudy and the many secondary endpoints in the no-ACEI patients in Val-HeFT could strengthen the subset findings further."

Novartis met with the Agency on December 13, 2001, and agreed at the meeting to submit the following:

- Retrospective analyses of how valsartan plus different doses (i.e., low & high) of ACE inhibitors affected morbidity and mortality endpoints.
- Retrospective analyses of the ETT (exercise tolerance test) sub-studies from trials 106 and 107 showing the effect of different doses of ACE inhibitors on morbidity and mortality endpoints.
- Any other analyses that would support approval of valsartan in the treatment of heart failure.

Dr. Temple noted that these analyses, when submitted, would be considered the firm's formal response to the approvable letter and the Agency would classify them as a type II resubmission (6 month PDUFA review clock).

Novartis on January 22, 2002 (our receipt date, January 23, 2002) submitted the retrospective analyses requested at the December 13, 2002 meeting. Consequently, the PDUFA action date became July 23, 2002. Revised draft labeling for both supplements was sent by the firm on February 12, 2002.

The telecon today was to discuss what action the Agency would take on the supplements by the July 23, 2002 goal date.

Telecon

Dr. Temple opened the telecon by noting that an approvable letter with, hopefully, draft labeling will be sent to the sponsor by the July 23, 2002 action date. The indication for valsartan will be for patients with CHF that are intolerant to ACE Inhibitors. Our mark-up of the draft labeling will mention the positive Val-Heft results for hospitalizations, but will note they were driven primarily by a small subset of patients in the study that did not receive an ACE Inhibitor. The no-ACE subset endpoints will be listed in the labeling but not the corresponding p values. The exercise tolerance test results from study 106 will not be listed. We will, however, describe the apparent negative interaction of valsartan when given to patients that are taking both an ACE inhibitor and beta blocker.

Novartis asked if valsartan could be indicated as a substitute for an ACE inhibitor rather than just in patients that are intolerant to ACE inhibitors. They also note that since there was a very positive effect on mortality in the no ACE group, trials employing an Angiotensin II antagonist for this indication will be very difficult to enroll. Dr. Temple replied that he is not comfortable labeling valsartan as a substitute for ACE inhibitors based on a subset finding of 300 or so patients when there are data on thousands of patients on ACE inhibitors that clearly show that it is effective in the treatment of heart failure.

Minutes Preparation: /S/
Edward Fromm

Concurrence, Chair: /S/
Robert Temple, M.D.

drafted/ef: 7/19/02-7/26/02-7/29/02

Rd: STargum-7/26/02
NStockbridge-7/26/02
DThrockmorton-7/26/02
NMorgenstern-7/26/02

Minutes of a Telecon between Novartis and the FDA

Date: September 25, 2001

Application: NDA's 20-665/SE1-016 & 21-283/SE1-001
Diovan (valsartan) Capsules and Tablets

Indication: Treatment of patients with CHF (Congestive Heart Failure)

Applicant: Novartis Pharmaceuticals Corporation

Subject: Pre-Advisory Committee Discussion

FDA participants

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Douglas Throckmorton, M.D., HFD-110, Deputy Division Director
Norman Stockbridge, M.D., Ph.D., Medical Team Leader
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Shari Targum, M.D., HFD-110, Medical Officer
Nhi Nguyen, Pharm.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Edward Fromm, HFD-110, Project Manager

Novartis

Jay Cohn, M.D., Val-HeFT Study Chairman
Malcolm MacNab, M.D., Ph.D., Vice President, Cardiovascular Clinical Research
Robert Glazer, M.D., Director, Heart Failure Team Leader
Tom Chiang, Ph.D., Director, Biostatistics
Pratapa Prasad, Ph.D., Manager, Clinical Pharmacokinetics
Adrian Birch, Executive Director, Drug Regulatory Affairs
Nancy Price, Associate Director, Drug Regulatory Affairs
Ayanna Abadie, Pharm.D., Fellow, Drug Regulatory Affairs

Background

Novartis, on April 27, 2001, submitted an efficacy supplement for valsartan capsules for the treatment of CHF. They subsequently submitted to their newly approved tablet NDA (21-283), on July 23, 2001, the clinical data for CHF as well as data to support a new 40 mg dosage strength. The firm was given a priority review for both supplements.

The Division asked Novartis to present their data for valsartan for CHF at the October Cardio-Renal Advisory Committee Meeting. The firm agreed to present before the Committee and requested this telecon to go over items that were likely to be discussed at the meeting.

Telecon

Dr. Lipicky opened the telecon by expressing doubts about the approvability of the application because although the ValHeft study had achieved nominal statistical significance on its primary endpoint, there were some internal inconsistencies with the data. For example, it appeared that study patients who were not taking ACE inhibitors had greater benefit than those that were taking ACE Inhibitors. Other subgroup analyses that showed considerable variance were patients studied in the United States versus those in foreign study sites and patients taking ACE

inhibitors and/or beta-blockers during the study. Therefore, the application would be unlikely to be approved based solely on its primary endpoint but could be approved if supported by positive secondary endpoint results and subgroup analyses. It will be important for the Advisory Committee to go through the secondary endpoints and subgroup analyses to ascertain whether a clinical benefit exists. Novartis noted that they plan to discuss the subgroup analyses in great detail at the Advisory Committee Meeting.

Dr. Lipicky commented that the progression of the disease did not appear to be altered by valsartan treatment and asked if the claimed effect on reducing hospitalizations for heart failure was a symptomatic or mortality benefit. The firm replied that valsartan's effect was probably in between a symptomatic or mortality claim; they believe that there is subgroup evidence pointing to a mortality benefit in patients that are not concurrently taking a ACE inhibitor or beta blocker.

Dr. Lipicky noted that it was not apparent whether valsartan exhibits a dose-dependant response. Novartis disagreed and said that study 104, for example, showed that 160 mg of valsartan exhibited a greater effect than 80 mg of the drug. Dr. Lipicky replied that there was a least one study that showed an absence of dose-response; he said that a graph of that study and possibly other studies would be faxed to the firm that would illustrate this fact.

Pediatric Waiver

Novartis asked if the Division had come to a decision about granting a pediatric waiver for valsartan for the heart failure indication. They pointed out that Toprol XL, an agent used for heart failure, recently received a pediatric waiver. Dr. Lipicky noted that Toprol XL was a controlled-release formulation and therefore not suitable for the pediatric population. He did say, however, that he would review the firm's pediatric waiver request and make a decision soon about granting a waiver or deferral.

Draft Questions for the Advisory Committee Meeting

Dr. Lipicky said that the Division would formulate draft questions for the Advisory Committee Meeting and would fax them to the firm for comment by Monday (October 1, 2001).

Minutes Preparation: /S/
Edward Fromm

Concurrence, Chair: /S/
Raymond Lipicky, M.D.

drafted/ef: 10-01-01

Rd: NNguyen-10-2-01
STargum-10-3-01
AKarkowsky-10-4-01
NStockbridge-10-4-01
DThrockmorton-10-5-01

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

Transmitted to FAX Number:	(973) 781-3590
Attention:	Ms. Nancy Price
Company Name:	Novartis
Phone:	(973) 781-3591
Subject:	**Confirmation of Meeting w/FDA** **NDA 21-283 & 20-665** **Valsartan for CHF**
Date:	07/30/01
Pages including this sheet:	**2**
From:	**Edward Fromm**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

Confirmation of Meeting

Drug:	NDA 20-665/SE1-016 Diovan (valsartan) Capsules for CHF NDA 21-283/SE1-001 Diovan (valsartan) Tablets for CHF
Sponsor:	Novartis
Subject:	Status of Reviews and October Advisory Committee Meeting
Date Requested:	July 25, 2001
Date Confirmation Faxed:	July 30, 2001
Meeting Date:	August 28, 2001
Meeting Time:	10:00 A.M.
Location:	conference Room "F", Fifth floor, Woodmont Office Complex 2 1451 Rockville, Pike, Rockville, MD

FDA Participants:

Douglas Throckmorton, M.D., HFD-110, Deputy Division Director
Norman Stockbridge, M.D., Ph.D., Medical Team Leader
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Shari Targum, M.D., HFD-110, Medical Officer
Nhi Nguyen, Pharm.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Patrick Marroum, Ph.D., HFD-860, Clinical Pharmacology and Biopharmaceutics, Team Leader
Natalia Morgenstern, HFD-110, Chief, Project Management Staff
Quynh Nguyen, Pharm.D., HFD-110, Project Manager
Edward Fromm, HFD-110, Project Manager

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

Transmitted to FAX Number:	(973) 781-3590
Attention:	Ms. Nancy Price
Company Name:	Novartis Pharmaceuticals Corporation
Phone:	(973) 781-3591
Subject:	**Minutes of meeting w/FDA, December 13, 2001** **Diovan (valsartan)** **NDA 20-665 (capsules)** **NDA 21-283 (tablets)**
Date:	January 15, 2002
Pages including this sheet:	10
From:	**Edward Fromm**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

Minutes of a Meeting between Novartis and the FDA

Date: December 13, 2001

Application: NDA's 20-665/SE1-016 & 21-283/SE1-001
Diovan (valsartan) Capsules and Tablets

Indication: Treatment of patients with CHF (Congestive Heart Failure)

Applicant: Novartis Pharmaceuticals Corporation

Subject: Submission of Retrospective Analyses following the Approvable Letter

FDA participants

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research
Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
Shari Targum, M.D., HFD-110, Medical Officer
James Hung, Ph.D., HFD-110, Statistician/Team Leader
Patrick Marroum, Ph.D., HFD-860, Clinical Pharmacology and Biopharmaceutics, Team Leader (pre-meeting only)
Thomas Marciniak, M.D., HFD-110, Medical Officer
Edward Fromm, HFD-110, Project Manager

Novartis

Jay Cohn, M.D., Val-HeFT Study Chairman
Malcolm MacNab, M.D., Ph.D., Vice President, Cardiovascular Clinical Research
Robert Glazer, M.D., Director, Heart Failure Team Leader
Tom Chang, Ph.D., Director, Biostatistics
Mathias Hukkelhoven, Vice President, Drug Regulatory Affairs
Adrian Birch, Executive Director, Drug Regulatory Affairs
Nancy Price, Associate Director, Drug Regulatory Affairs

Background

Novartis, on April 27, 2001, submitted an efficacy supplement for valsartan capsules for the treatment of CHF. They subsequently submitted to their newly approved tablet NDA (21-283), on July 23, 2001, the clinical data for CHF as well as data to support a new 40 mg dosage strength. The firm was given a priority review for both supplements.

Novartis believed that valsartan, when used as an add-on to existing therapy (ACE Inhibitors, beta-blockers) for heart failure significantly reduced the risk for the primary endpoint of time to first morbid event, defined as all-cause mortality, heart failure hospitalization, sudden death with resuscitation, and need for intravenous vasodilator or inotropic therapy compared to placebo. They also believe that the drug has a favorable effect on selected secondary endpoints chosen in the studies.

These supplements were the subject of an October 11, 2001 meeting of the Cardio-Renal Advisory Committee Meeting. The Committee voted 4 to 4 on whether to approve valsartan for the treatment of chronic heart failure. Complicating the decision were subgroup analyses of people already on an ACE inhibitor (over 90% of the patients) that showed a very small positive effect on morbidity and essentially no effect on mortality. Moreover, patients

taking a Beta-Blocker as well as an ACE inhibitor seemed to show a small, negative mortality effect. On the other hand, there were large and statistically strong effects of valsartan in patients not on an ACE inhibitor.

The Agency decided that there was not enough evidence to show that valsartan was appropriate to be added on to patients currently receiving ACE inhibitors and/or beta blockers. There was subset evidence, however, that indicated that valsartan could be used as a substitute for ACE inhibitors in the treatment of heart failure. Therefore, the Agency issued an approvable letter on October 24, 2001 noting that valsartan was "approvable" as a substitute for ACE Inhibitors in heart failure and asked the firm to submit additional, retrospective analyses of the data that could support approval. These analyses were submitted on November 29, 2001 and are the subject of this meeting.

Meeting

Regulatory Considerations

Dr. Temple opened the meeting by noting that the Agency has not made a final decision on whether to approve valsartan for the treatment of heart failure on the basis of the available data. Because the overall trial results were positive for valsartan on the primary endpoint, we have some "permission" to look at subsets. Valsartan, when used in patients not on an ACE inhibitor, in just a few hundred patients not on ACE inhibitors, had favorable effects on survival and hospitalization as well as exercise tolerance and symptoms.

The Agency, however, is cautious on approving valsartan for this indication based on essentially a favorable subset of a study, even though the overall study is generally positive for morbidity. Does that effect mean it is permissible to look at mortality in the non-ACE inhibitor subset when the overall mortality effect for the trial was essentially neutral?

Indication for Valsartan

Another issue the Agency is struggling with is the patient population for which the drug would be indicated. Should it be indicated as a substitute for ACE inhibitors in heart failure or just for ACE inhibitor-intolerant patients? Dr. Temple stated that he believes that the drug should be indicated only for ACE intolerant patients because there were just 366 patients in the no ACE-ValHeft subset compared with data on thousands of patients on ACE inhibitors that clearly show that it is effective in the treatment of heart failure. The Val-Heft data also seem to indicate that adding valsartan to an ACE inhibitor and beta-blocker cannot be recommended and, indeed, should be discouraged.

Novartis believes that the indication for valsartan should be as an alternative to an ACE inhibitor and as an add-on to an ACE inhibitor or beta-blocker, but not to a combination of ACE inhibitor and beta-blocker until further data are available. They noted that they currently have the VALIANT study underway, in which patients that have had an acute myocardial infarction are being treated with valsartan alone, captopril alone, or a combination of valsartan and captopril. They indicated that about 70% of the patients are on beta-blockers as background therapy and have been allowed to continue this use by the DSMB (Data Safety Monitoring Board) even though valsartan appeared to have a negative mortality effect in the ValHeft trial when used with both an ACE inhibitor and beta-blocker. Therefore, by 2003 or 2004 (the trial's projected end date) they hope to have information that will show that is safe and effective to use valsartan with both an ACE inhibitor and beta-blocker.

Novartis presented a slide (S-2) that they believe shows that patients that received valsartan and low doses of ACE inhibitors in the ValHeft study also achieved favorable mortality and morbidity outcomes. It is even possible that some sort of dose-effect relationship could be demonstrated with further reanalyzes of the data. Dr. Temple encouraged the firm to send in any analyses that it thinks will demonstrate that valsartan, when added to ACE inhibitors (especially in low doses) contributes to positive morbidity and/or mortality outcomes. This information may also provide an answer as to why there seems to a negative mortality effect when valsartan is added to both an

ACE inhibitor and beta blocker. Dr. Temple added that if the firm has exercise tolerance data for the low dose and high dose ACE inhibitor use for studies 106 and 107 they should submit this information to the Division.

Submission of Analyses

Dr. Temple said the firm should send in the analyses asked for at today's meeting and any other others that may support the drug's approval for heart failure. When this submission comes in the Agency will consider it the firm's formal response to the approvable letter.

Novartis asked if this submission would be classified as a type I (2 month PDUFA clock) or II (6 month clock) resubmission. Dr. Temple said that we would classify this response as a type II resubmission and may discuss it with others in the Agency before making a final decision regarding approval.

Summary of Main Action Items

Novartis agreed to send the Division, in a timely manner, the following:

- Retrospective analyses of how valsartan plus different doses (i.e., low & high) of ACE inhibitors affected morbidity and mortality endpoints.
- Retrospective analyses of the ETT (exercise tolerance test) sub-studies from trials 106 and 107 showing the effect of different doses of ACE inhibitors on morbidity and mortality endpoints.
- Any other analyses that would support approval of valsartan in the treatment of heart failure.

When submitted, the Agency will consider these analyses the firm's formal response to the approvable letter and will classify them as a type II resubmission (6 month PDUFA review clock).

Minutes Preparation: /S/

Edward Fromm

Concurrence, Chair: /S/

Robert Temple, M.D.

drafted/ef: 12-21-01/1-08-02/1-14-02

Rd: TMarciniak-12-21-01
PMarroum-12-21-01
JHung-12-26-01
STargum-12-26-01
NStockbridge-12-27-01
AKarkowsky-1-7-02

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MESSAGE CONFIRMATION

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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

Transmitted to FAX Number: (973) 781-3590

Attention: Ms. Nancy Price

Company Name: Novartis Pharmaceuticals Corporation

Phone: (973) 781-3591

Subject: **Minutes of meeting w/FDA, December 13, 2001**
Diovan (valsartan)
NDA 20-665 (capsules)
NDA 21-283 (tablets)

Date: January 15, 2002

Minutes of a Meeting between Novartis and the FDA

Date: August 28, 2001

Application: NDA's 20-665/SE1-016 & 21-283/SE1-001
Diovan (valsartan) Capsules and Tablets

Indication: Treatment of patients with CHF (Congestive Heart Failure)

Applicant: Novartis Pharmaceuticals Corporation

Subject: Pre-Advisory Committee Meeting

FDA participants

Douglas Throckmorton, M.D., HFD-110, Deputy Division Director
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Shari Targum, M.D., HFD-110, Medical Officer
Nhi Nguyen, Pharm.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
James Hung, Ph.D., HFD-110, Statistician/Team Leader
Stuart Zimmerman, Ph.D., HFD-810, Chemist (pre-meeting only)
Quynh Nguyen, Pharm.D., HFD-110, Project Manager (pre-meeting only)
Edward Fromm, HFD-110, Project Manager

Novartis

Jay Cohn, M.D., Val-HeFT Study Chairman
Malcolm MacNab, M.D., Ph.D., Vice President, Cardiovascular Clinical Research
Reynu Gupta, M.D., Vice President, Clinical Research and Development
Robert Glazer, M.D., Director, Heart Failure Team Leader

Tom Chang, Ph.D., Director, Biostatistics
Pratapa Prasad, Ph.D., Manager, Clinical Pharmacokinetics
Adrian Birch, Executive Director, Drug Regulatory Affairs
Nancy Price, Associate Director, Drug Regulatory Affairs
Ayanna Abadie, Pharm.D., Fellow, Drug Regulatory Affairs

Background

Novartis, on April 27, 2001, submitted an efficacy supplement for valsartan capsules for the treatment of CHF. They subsequently submitted to their newly approved tablet NDA (21-283), on July 23, 2001, the clinical data for CHF as well as data to support a new 40 mg dosage strength. The firm was given a priority review for both supplements.

Novartis believes that valsartan significantly reduced the risk for the primary endpoint of time to first morbid event, defined as all-cause mortality, heart failure hospitalization, sudden death with resuscitation, and need for intravenous vasodilator or inotropic therapy compared to placebo. They also believe that the drug has a favorable effect on selected secondary endpoints chosen for the study.

The Division asked Novartis to present their data for valsartan for CHF at the October Cardio-Renal Advisory Committee Meeting. The firm agreed to present before the Committee and requested feedback on a draft background package for the meeting as well as the review of the application to date by the Division.

Meeting

Dr. Throckmorton noted that the October Cardio-Renal Advisory Committee meeting was scheduled for October 11th or 12th and reminded the firm of the September 10, 2001 deadline for submitting their briefing materials to Advisors and Consultants. He said that the different review disciplines had comments about the application and these are as follows:

Chemistry

Stability data was submitted for [redacted] (i.e., physician samples-Vol 4.3, p.4-416) and was not sufficient to support the [redacted] expiration dating that the firm desired. Dr. Throckmorton encouraged the firm to talk as soon as possible to Dr. Zimmerman about submitting additional stability data to support the [redacted] expiration date.

Biopharmaceutics

Dr. Nguyen said that her review was completed and that the firm will be granted a bioequivalency waiver for the 40 mg tablet strength. She noted that the dissolution specifications would be the same as for the already approved tablet strengths.

Novartis asked if they should have some slides prepared for the Committee Meeting that discussed the pharmacokinetic (PK) profile of valsartan in CHF. Dr. Throckmorton replied that it is possible that one of the committee members may have questions about the PK characteristics of the drug and therefore advised having some data available for discussion.

Clinical

- Dr. Throckmorton asked how were the events in the trial adjudicated (i.e., were all Case Report Forms (CRF's) sent to the Endpoint Committee). The firm said that with an event that was clearly non-cardiovascular (non-CV) related, a narrative of the event was sent to Endpoint Committee chairman who made a decision whether the event was truly non-cardiovascular or whether more information was needed. In the case of events that might be classified as either cardiovascular (CV) or non-CV related, tabular summaries of the CRF's, Serious Adverse Event forms, and hospital discharge summaries were sent to the Endpoint Committee. If the event was death, a narrative was included in addition to the above information.

- Dr. Targum said that based on an amendment to the Endpoint Committee manual, she was uncertain how overdiuresis and drug toxicity were defined as events. The firm said they were uncertain about these definitions and promised to send this information to the Division.

- Dr. Targum requested that narratives that were non-CV related and were sent to the Endpoint Committee should be sent to the Division for review. The firm indicated they would send the narratives in by next week.

- The Division expressed concern that non-heart failure hospitalizations might not be distributed equally between the groups classified as time to all-cause hospitalizations and first-time hospitalizations for CHF. Novartis argued that non-heart failure hospitalizations are almost identical in the two groups; they said they would send in additional detailed information explaining this similarity.

- The Division requested additional clarification on the numbers of events that were adjudicated centrally and those done by the study investigators.

Dr. Hung said that SAS codes were needed for those events defined as first-time hospitalizations. The firm indicated these codes would be sent in next week.

Dr. Hung noted that the firm used point estimates based on covariates when doing their statistical analyses. He mentioned that his numbers might be slightly different because he was doing unadjusted analyses based on the nominal p-values. The unadjusted analyses are consistent with the primary test the sponsor used.

- Dr. Throckmorton asked that CRF's listing angioedema as an adverse event should be sent in to the Division for further review. Effects such as facial, tongue, and lip swelling are examples of what should be classified as angioedema.

- Dr. Throckmorton noted that renal failure adverse effects seen in the studies were difficult to summarize and he suggested that the firm attempt to do this in their briefing document. He asked if any patients in the studies had progressed to dialysis treatment. Novartis said they are currently doing this analysis and will send in this information in to the Division.

- Dr. Karkowsky noted that there was little information about the doses of beta-blockers and ACE Inhibitors given with valsartan in the studies. The firm replied that they were in the process of going back to the CFRs to get that information; they noted that they plan to do an analysis based on that information to see if there were any trends in dosing changes among the groups.

  Dr. Throckmorton asked if the firm had analyzed the effect of concomitant therapy with spironolactone during the trials. The firm said that about 5% of the patients were taking spironolactone but said that it made no difference in the final results.

  Novartis asked how much importance should they give the subgroup analyses of valsartan with other drug groups when presenting at the Advisory Committee meeting. Dr. Targum believes that these analyses are important because background therapy is an integral part of the standard of care for CHF patients.

  The firm asked if the subgroup analyses regarding concomitant drug therapy would be part of the labeling. Dr. Throckmorton said it is difficult to say what will be included in the labeling but added that, in general, the subgroup analysis results would have to be highly significant for inclusion in the labeling.

Pediatrics

The Division in unsure of whether to grant a waiver or defer studies for the CHF indication for valsartan in response to the Pediatric Rule. Dr. Throckmorton said that Dr. Lipicky is considering bringing this issue before the October Advisory Committee for their advice on how one would go about designing trials in CHF for this population. Novartis expressed concern that this subject could involve significant discussion time at the meeting and suggested that this topic should be given a separate day for discussion. They also noted that other pharmaceutical firms and patient advocacy groups should be given input in this discussion. Dr. Throckmorton agreed these were valid points and would bring these to Dr. Lipicky's attention. He added that the firm should not address the pediatric question in any of their briefing documents.

Other Advisory Committee Items

The firm asked whether they should include draft labeling in their briefing document. Dr. Throckmorton said it would be better for the firm to present a slide(s) to the committee during their presentation indicating what they would like to include in the labeling.

Dr. Throckmorton said the Division is not planning to make a presentation at the Advisory Committee Meeting but ted that its briefing book will be sent to the firm by Advisors and Consultants. He also said the Division was open meeting with the firm prior to the Advisory Committee meeting if necessary.

Summary of Main Action Items

Novartis agreed to send the Division, in a timely manner, the following:

- Data to demonstrate equality between the distribution of non-CV hospitalizations between time to all-cause hospitalizations and first hospitalizations for CHF
- CRFs for angioedema in the studies
- Better summaries of the renal adverse effects; did any of the patients require dialysis?
- SAS codes for first-time hospitalizations
- Non-CV narratives that were sent to the Endpoint Committee
- Clarification on the amendment to the Endpoint Committee manual regarding overdiuresis and drug toxicity
- A detailed explanation of the adjudication process in the studies. This should include a breakdown of what events that were adjudicated centrally and those done by the study investigators
- Information of what the exact doses of beta-blockers and ACE Inhibitors patients were receiving during the studies.

Minutes Preparation: _____
Edward Fromm

Concurrence, Chair: _____ 9 5.26.01
Douglas Throckmorton, M.D.

ed/ef: 8-29-01/9-26-01

Rd: SZimmerman-8/29/01
NNguyen-9/05/01
JHung-9/5/01
STargum-9/6/01
AKarkowsky-9/9/01

Minutes of a NDA Efficacy Supplement Filing Meeting

Date:	June 7, 2001
Application:	NDA 20-665/SE1-016 Diovan (valsartan) Capsules for CHF 80 and 160 mg
Applicant:	Novartis Pharmaceuticals
Application Date:	April 27, 2001
Receipt Date:	April 27, 2001
User Fee Goal Date:	October 27, 2001

Participants:

Douglas Throckmorton, M.D., HFD-110, Deputy Division Director
Norman Stockbridge, M.D.,Ph.D., HFD-110, Medical Team Leader
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Shari Targum, M.D., HFD-110, Medical Officer
James Hung, Ph.D., HFD-110, Statistician/Team Leader
Anthony Proakis, Ph.D., HFD-110, Pharmacologist
Stuart Zimmerman, Ph.D., HFD-810, Chemist
Nhi Nguyen, Pharm.D., HFD-860, Biopharmaceuticist
Howard Lee, M.D. HFD-110, Research Fellow
Jesse Taur, HFD-110, Research Fellow
Andrew Haffer, Pharm.D., HFD-042, DDMAC,
Quynh Nguyen, Pharm.D., HFD-110, Project Manager
Natalia Morgenstern, HFD-110, Chief, Project Management Staff
Edward Fromm, HFD-110, Project Manager

Background

Novartis has submitted this efficacy supplement for valsartan for CHF. Valsartan, an angiotensin II receptor blocker, is currently indicated for the treatment of hypertension. Studies for valsartan for CHF were conducted under IND [redacted].

The application for efficacy and safety is supported principally by 4 placebo (#'s 103, 104, 106 and 107-Val-HeFT) and 1 active controlled (#110) studies. Novartis claims that valsartan significantly reduced by 13.2% the primary endpoint of time to first morbid event, defined as all-cause mortality, heart failure hospitalization, sudden death with resuscitation, and need for intravenous vasodilator or inotropic therapy when compared to placebo. They also claimed that valartan lessened the time to first heart failure hospitalization (compared to placebo) and exerted significant beneficial effects on a variety of symptomatic endpoints.

The company requested a priority review for this supplement because they believe that Diovan demonstrated a benefit versus placebo in patients treated with existing therapies for heart failure. Dr. Lipicky has decided that the application qualifies for a priority review because the drug could be of benefit in patients who have tried all other CHF therapies.

Meetings

End-of Phase 2: January 13, 1994 (CHF indication discussed)

Meeting

Pharmacology

Reviewer: Anthony Proakis, Ph.D.

Dr. Proakis had no objections to filing the NDA. He said that there were no pharm/tox changes to the labeling and therefore a formal review would not be necessary.

Chemistry

Reviewer: Stuart Zimmerman

Dr. Zimmerman had no objections to filing the NDA. He said that it appears that the 40 mg tablet has stability problems which could become an issue in terms of assignment of an expiry date equal to that of the other tablet strengths if the firm supplements NDA 21-283 ("tablet NDA for hypertension") for the CHF indication. **Note:** Novartis plans on supplementing NDA 21-283 with a CHF indication and a 40 mg tablet strength once it is approved in the summer of 2001. The firm would cross reference the 20-665 application for the clinical data to support the CHF indication.

Dr. Zimmerman said he expected his review to be completed by September 1, 2001.

Biopharmaceutics

Reviewer: Nhi Nguyen, Pharm.D.

Dr. Nguyen had no objections to filing the NDA. She said that there are 2 PK studies in this supplement. Information needed to support a waiver for the 40 mg tablet (when submitted to NDA 21-283) are: individual and mean dissolution data and F2 calculation.

Dr. Nguyen expects her review to be completed by September 1, 2001

Statistical

Reviewer: James Hung, Ph.D.

Dr. Hung had no objections to filing the NDA. His review will focus on studies 106 and 107. The review is expected to be completed by September 1, 2001.

Medical

Medical Officers: Shari Targum, M.D.
Abraham Karkowsky, M.D., Ph.D.

Dr. Targum will review the safety as well as the efficacy studies 102, 103, 104, 106 and 107 while Dr. Karkowsky will review study 110. They expect their reviews to be completed by September 1, 2001.

Secondary Medical Review

Reviewer: Norman Stockbridge, M.D., Ph.D.

Dr. Stockbridge expects to complete his review by September 7, 2001.

Division of Scientific Investigations

The Division does not believe audits are needed for the studies supporting this supplement, but Dr. Rios of DSI indicated, subsequent to the filing meeting, that they would conduct audits of studies 106 and 107.

Advisory Committee Meeting

This supplement may be the subject of the October, 2001, Cardio-Renal Advisory Committee Meeting.

Conclusion

The application will be filed. The supplement may be presented at the October Cardio-Renal Advisory Committee Meeting.

Minutes Preparation: /S/
Edward Fromm

Concurrence Chair: /S/
Douglas Throckmorton, M.D.

dr: ef/6-13-01/8-06-01

Rd:
QNguyen-6-13-01
AProakis-6-13-01
SZimmerman-6-21-01
NNguyen-6-21-01
JTaur-6-21-01
JHung-6-21-01
STargum-6-25-01
AKarkowsky-6-25-01
NStockbridge-7-27-01
DThrockmorton-7-27-01
NMorgenstern-8-3-01

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Minutes
April 29, 1996
End-of-Phase II Meeting
IND [redacted] Valsartan - Angiotensin II Receptor Antagonist
for the treatment of Congestive Heart Failure
Ciba-Geigy Corporation

Pre-meeting submission: April 5, 1996, serial number 021

Attending:

Ciba-Geigy:

Malcolm MacNab, M.D., Ph.D.	Vice President, Cardiovascular Development
Marjorie Gatlin, M.D.	Director, Clinical Research
Robert Glazer, M.D.	Assoc. Director, Clinical Research
Tom Chiang, Ph.D.	Manager, Biostatistics
Barbara Shroff	Director, Drug Regulatory Affairs
Nancy Price	Manager, Drug Regulatory Affairs

FDA:

Raymond Lipicky, M.D.	HFD-110	Division Director/Chair
Shaw Chen, M.D., Ph.D.	HFD-110	Group Leader/Medical
Charles Ganley, M.D.	HFD-110	Medical Officer
Maryann Gordon, M.D.	HFD-110	Medical Officer (observer)
Walid Nuri, Ph.D.	HFD-710	Statistician
Parnian Zia-Amirhoissini, Ph.D.	HFD-860	Biopharmaceutist
Kathleen Bongiovanni	HFD-111	Regulatory Health Project Manager /Minutes Preparer

Background: Ciba Geigy has submitted NDA 20-665 for valsartan for the treatment of hypertension. They are also investigating its use for the treatment of congestive heart failure (CHF) under IND [redacted] They asked to come in for an End-of-Phase II Meeting for the CHF indication.
[Dr. Temple was unavailable for the meeting and told us to have it without him.]

Meeting Objectives:

- Evaluate Phase III plan and protocols
- Discuss labeling objectives

Discussion Points:

Endpoints

Dr. Lipicky pointed out that choosing an appropriate endpoint in CHF trials for this class of drugs is difficult. He noted that although a combined endpoint is not an unwise choice, if not all parts of the combined endpoint have results in the same direction there may be approvability issues.

Ciba asked whether we would still approve a drug based on two positive exercise tolerance testing (ETT) trials, without a mortality determination. Dr. Lipicky said that we would. In this case, labeling would be similar to the labeling for ACE inhibitors that are approved for the treatment of CHF without showing a mortality effect.

There was a discussion about the inability of ETT trials to give positive results. Dr. Lipicky suggested that large trials with hospitalization for CHF as an endpoint may have a greater chance of showing a benefit from the drug than ETT trials. For Protocol 106, he agreed with the firm's suggestion to use the Minnesota Living with Heart Failure Questionnaire as a primary, rather than a secondary, endpoint, or using a combined endpoint.

Dr. Ganley suggested that the firm revise Protocol 106 to have patients who drop out of the trial have an ETT at the time they drop out.

p Values

There was a discussion of what the appropriate p value would be if approval would be based on only one trial. Dr. Lipicky said that he would encourage the value to be closer to $p=0.05^2$ than to p=0.05. Approval based on one trial would need robust results, dose-related effects, or other reasons to believe that the results are reproducible.

Ciba proposed terminating Protocol 107 after 1233 events. If after 4 years 1233 events are not reached, Ciba would like the option of terminating the trial, allowing the trial to continue until 1233 events are accrued, or lengthening the duration of the trial. Dr. Ganley noted that if the sponsor has any knowledge of treatment effect data when making this decision or if the termination results in a declaration of efficacy, then this would constitute an interim analysis and some alpha spending should occur.

Trial Design

Dr. Lipicky encouraged the firm to use higher doses in their protocols.

Ciba said that they are planning to enroll NYHA Class II -IV (predominantly II and III) in Protocol 106 and NYHA Class III and IV patients in Protocol 107, and they asked whether the drug would be labeled as having a mortality benefit only in NYHA Class III and IV, given positive results. Dr. Lipicky said that he would not make a distinction between Class III and IV and all patients, but there may be some disagreement.

Ciba asked about stratifying patients as having ischemic versus non-ischemic heart failure. Dr. Lipicky said that if they do not stratify, they run the risk of having unbalanced groups.

Conclusions:

Protocol 106:

- The firm will consider changing the primary endpoint from exercise tolerance testing to the Minnesota Living with Heart Failure Questionnaire score or to a combined endpoint.

Protocol 107:

- Ciba will revise the stopping rule to base it on mortality alone.
- The number of events that will determine when the interim analysis will be performed will be specified as either 700 or 800.
- The protocol will specify either that an independent group will send the Data and Safety Monitoring Board data for all analyses, or that if someone in the firm will have access to the data from the interim analysis or any other time, the look at the trial data at 4 years

will be considered a second interim analysis and appropriate statistical penalties will be calculated.

- The firm will consider having two primary endpoints, both all-cause mortality and the combined endpoint; in this case, the alpha level will be recalculated.

- The firm will consider what p value they should achieve if the approval of valsartan for congestive heart failure will be based on only this trial.

Other:

- The firm will send a sealed copy of the randomization codes for both trials to their IND.

- The firm will provide pharmacokinetic data from congestive heart failure patients given BID dosing.

- The labeling will reflect the results of the trials upon which the approval is based.

Signature, minutes preparer: _____ 5-10-96
Kathleen F. Bongiovanni

Concurrence Chair (or designated signatory): _____

cc: IND
HFD-110
HFD-111/KBongiovanni
HFD-111/SBenton
kb/5/1/96; 5/3/96.
R/D: CGaffney/5/1/96; SChen/5/1/96; WNuri/5/2/96; Zia-Amirhoissini/5/2/96.
5/13/96

KB

JUL 12 100

Telephone Conference
July 7, 1994
IND — valsartan - Angiotensin II Receptor Antagonist
for the treatment of congestive heart failure

FDA:

Raymond J. Lipicky, M.D.	HFD-110	Division Director
Robert R. Fenichel, Ph.D., M.D.	HFD-110	Group Leader/Medical
Steve Rodin, M.D.	HFD-110	Medical Officer
Karen Frank, M.D.	HFD-110	FDA Fellow
Kathleen Bongiovanni	HFD-111	Consumer Safety Officer

Ciba-Geigy:

Nancy Price	Manager, Cardiovascular Drug Regulatory Affairs
Malcolm MacNab, M.D., Ph.D.	Vice President, Cardiovascular Drug Development
Jorie Gatlin, M.D.	Director, Cardiovascular Clinical Research
Robert Glazer, M.D.	Associate Director, Cardiovascular Clinical Research
Yann-Tong Chiang, Ph.D.	Biostatistician

Background: Ciba is studying valsartan for the treatment of congestive heart failure (CHF). They have an opportunity to participate in a study that will be conducted by the Vasodilator-Heart Failure Veterans Affairs Cooperative Study Group (VHeFT), VHeFT-IV.

The study is a randomized, double-blind, placebo-controlled, forced titration study of 3-4 years duration in approximately 600 to 1,000 NYHA Class II-IV patients. There will be one trial in patients on a background of ACE inhibitors, diuretics, and digoxin, and another in patients who are intolerant to ACE inhibitors, on a background of diuretics and digoxin. Ciba submitted an outline of the trials in their correspondence dated June 23, 1994, serial number 005.

They asked for this telephone conference to discuss the acceptability of the proposed VHeFT IV trials as the two adequate and well-controlled trials for a supplement for CHF.

Telephone Conference:
Ciba began by saying that they plan to treat the two arms of the VHeFT-IV trial as two separate trials. In addition, they plan to conduct two Phase II trials, a dose-ranging trial on a background of ACE inhibitors with hemodynamic endpoints and an angiotensin II challenge study to see if angiotensin II receptors are upregulated. The results from the dose-ranging trial will be used to determine the doses for VHeFT-IV.

They said that the endpoints for the arm of VHeFT-IV with patients on a background of ACE inhibitors will have a combined endpoint including morbidity and mortality components as well as exercise tolerance testing (ETT). The arm with patients intolerant to ACE inhibitors will use exercise tolerance as an endpoint, since they do not believe that they will be able to find enough patients intolerant to ACE inhibitors to increase the sample size to allow for a mortality endpoint.

The firm asked for our opinion of their development plans.

Dr. Lipicky said that if the results are spectacular, such as having a p of less than 0.0025 for mortality, we would be obligated to do "nice things." Otherwise, we would have to think a long time about what to do with the supplement.

Ciba asked what else might be needed for an approvable package. Dr. Lipicky said that the answer would require some thought. He said that about half of all trials in CHF using ETT as an endpoint with drugs that are useful in CHF fail to find a statistically significant difference between drug and placebo. So he would encourage them to have two or more trials with exercise endpoints.

In addition, he said that he is uncomfortable with the prospect of having a positive mortality endpoint in a trial that studied only one dose. He said that we encourage firms to conduct dose-ranging morbidity/mortality trials. He added that in the treatment of CHF, it is reasonably clear that the doses that may increase ETT time or hemodynamics may not necessarily be the doses that have a positive effect on morbidity and mortality; they will need a point estimate of the effect on mortality even if they are not seeking a mortality claim. He said that we are not comfortable with a single trial with a mortality endpoint unless the results are fairly spectacular.

Ciba asked whether the ETT trial would be supportive of the mortality trial. Dr. Lipicky said no, the effects are independent of each other.

Dr. Lipicky said that we would be uncomfortable if VHeFT-IV was the only source of data. Ciba asked whether we would accept VHeFT-IV plus two or more ETT trials. Dr. Lipicky said that was likely, but we would need to know the design of the trials in more detail.

Ciba thanked us for the time and said that they will have more discussions with us on their development plans.

S

Kathleen Bongiovanni 7-12-94

cc: IND
HFD-110
HFD-111/KBongiovanni
HFD-111/SBenton
kb/7/11/94; 7/12/94.
R/D: KFrank/7/11/94; SRodin/7/11/94; RRFenichel/7/11/94.

MESSAGE CONFIRMATION

07/30/01 11:13
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Rockville, MD 20857

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1451 Rockville Pike
Rockville, MD 20852

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Attention: Ms. Nancy Price

Company Name: Novartis

Phone: (973) 781-3591

Subject: **Confirmation of Meeting w/FDA**
NDA 21-283 & 20-665
Valsartan for CHF

Date: 07/30/01

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Attention:	Ms. Nancy Price
Company Name:	Novartis Pharmaceuticals
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Subject:	**Approval Letter for NDA 20-665/S-016 & NDA 21-283/S-001**
Date:	August 14, 2002
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SECOND APPROVABLE Letter

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Transmitted to FAX Number:	(973) 781-3590
Attention:	Ms. Nancy Price
Company Name:	Novartis Pharmaceuticals
Phone:	(973) 781-3591
Subject:	**Approvable Letter w/Marked-up Draft Labeling for NDA 20-665/S-016 & NDA 21-283/S-001**
Date:	July 23, 2002
Pages including this sheet:	**29**
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Rockville, MD 20857

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1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(973) 781-3590
Attention:	Ms. Nancy Price
Company Name:	Novartis Pharmaceuticals Corporation
Phone:	(973) 781-3591
Subject:	**Minutes of Telecon w/FDA, July 18, 2002** **Diovan (valsartan)** **NDA 20-665/S-016 (capsules)** **NDA 21-283/S-001 (tablets)**
Date:	August 1, 2002
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