CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-665/S-016
NDA 21-283/S-001

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-665/S-016
NDA 21-283/S-001

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

Dear Ms. Price:

Please refer to your supplemental new drug applications dated April 27 (NDA 20-665) and July 23, 2001 (NDA 21-283), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diovan (valsartan) Capsules, 80 and 160 mg (NDA 20-665) and Tablets, 40, 80, 160, and 320 mg (NDA 21-283).

We acknowledge receipt of your submissions dated July 25 and 29, 2002. Your submissions of July 29, 2002 constituted a complete response to our July 23, 2002 approvable letter.

These supplemental new drug applications provide for the use of Diovan (valsartan) Capsules and Tablets for the treatment of heart failure (NYHA class II-IV) in patients who are intolerant to an ACE (angiotensin converting enzyme) inhibitor. In addition, NDA 21-283/S-001 provides for a new 40 mg tablet strength.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (package insert included in your submissions of July 29, 2002, immediate container and carton labels included in your submission of June 17, 2002). Accordingly, these supplemental applications are approved effective on the date of this letter.

Please make the following changes to the labeling at your next printing:

1. (NDA 20-665/S-016)-Under **DESCRIPTION**, 5th sentence, please add after iron oxides, in parantheses, 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).

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, 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 (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies for this indication until September 30, 2007. However, in the interim, please submit your pediatric drug development plans within 180 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

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

Sincerely,

/S/

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures: Final Printed Labeling for NDA's 20-665/S-016 & 21-283/S-001

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/s/

Robert Temple
8/14/02 02:25:38 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 20-665/S-016
NDA 21-283/S-001

Approvable Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-665/S-016
NDA 21-283/S-001

Novartis Pharmaceuticals Corporation
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One Health Plaza
East Hanover, New Jersey 07936-1080

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We acknowledge receipt of your submissions dated October 30, November 28, and December 18, 2001 and January 22 and 25, February 12, March 14, and June 17, 2002.

These supplemental new drug applications provide for the use of Diovan (valsartan) Capsules and Tablets for the treatment of heart failure (NYHA class II-IV) in patients who are intolerant to an ACE (angiotensin converting enzyme) inhibitor. In addition, NDA 21-283/S-001 provides for a new 40 mg tablet strength.

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed marked-up draft labeling.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit the copies of final printed labeling (FPL) electronically (to each application) according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL (to each application), ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These drug products may not be legally marketed for this indication until you have been notified in writing that these supplements are approved.

If you have any questions, please contact:

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

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures: Marked-up Draft Labeling for NDA's 20-665/S-016 & 21-283/S-001

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

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/s/

Robert Temple
7/23/02 06:19:49 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-665/S-016
NDA 21-283/S-001

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We acknowledge receipt of your submissions to NDA 20-665 dated May 7, 21, and 29, June 13, 27 and 28, July 12, August 1, 2, 13, 16, 17, 20, 24, 29, 30, and 31, September 7 (three), 13, and 19, October 19 and 22, 2001 and to NDA 21-283 dated August 1 and 16, 2001.

These supplemental new drug applications provide for the use of Diovan (valsartan) Capsules and Tablets for the treatment of heart failure (NYHA class II-IV) to reduce morbidity, primarily via reduction in hospitalizations for heart failure. In addition, a new 40 mg tablet strength has been established.

We have completed the review of these applications, as amended, and because there is one study providing evidence that valsartan may substitute for an angiotensin-converting enzyme inhibitor (ACEI), valsartan is approvable for such a use. As will be explained below, however, we do not believe there is preliminary evidence that valsartan is effective when added to adequate doses of an ACEI and believe that a second study is needed to confirm the effect of valsartan in patients not receiving an ACEI. Because it is not yet possible to describe the labeling that might be approved with further data, we are not providing marked-up draft labeling at this time.

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

1. The Val-HeFT Study Design

   Val-HeFT was a well-designed, multicenter, multinational, large (n=5010) placebo-controlled trial comparing valsartan 320 mg (if tolerated) with placebo in patients with symptomatic CHF and EF < 40%, LVID > 2.9 cm/m^2. This was a "real world" study and participating physicians determined the background treatment for CHF, including ACEI's (most), beta blockers (about one-third), diuretics (most), digoxin, nitrates (about one third), and spironolactone (about 5%). The doses of background therapy were not specified and were also chosen by study participants.

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

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

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

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

(2) AII blockade could substitute for ACE inhibition. The theoretical support for this effect seems quite strong.

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

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

2. Val-HeFT Results

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

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

As you can see, we do not have complete data on the patients divided by ACE/no ACE but a preliminary

analysis of the ACE yes vs. ACE no results for signs and symptoms suggests that for almost every case the HR was more favorable for the No ACE group.

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

3. Evaluation

a. Use in addition to standard therapy

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

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

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

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

b. Use as a substitute for an ACEI

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

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

Please note that the 40 mg tablet should have similar dissolution specifications as the other approved tablet strengths:

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

Please be advised that based on the stability data provided, we will permit the following expiration dating for your 40 mg tablet:

a. 18 months for blister packaging and physician samples
b. 24 months for — bottle trade packages

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Robert Temple
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