CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-283/S011

Approvable Letter (s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-283/S-011

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 application dated 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 acknowledge receipt of your submissions dated January 12, 20 and 26, February 4, 10, and 20 (two), March 18 and 30 (two), April 19 and 29, May 6, 13, 25, and 28 (two), June 25, August 3 and 19, September 3, 20, and 23, October 1, 8, and 27, November 30, and December 21, 22, and 29, 2004.

This supplemental new drug application proposes the use of Diovan (valsartan) 40, 80, 160, and 320 mg Tablets in the treatment of patients post myocardial infarction (MI) who are intolerant to ACE inhibitors.

We have completed our review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary to develop final printed labeling (FPL) for the drug. Final printed labeling cannot be submitted until the issues described below are addressed. When you respond to the following concerns you should submit modified proposed labeling.

You will need to address why the VALIANT study 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.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. 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, MD 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. 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.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes before approval of this supplemental application.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5328

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
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____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling