CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-387/S-013, 015 & 027

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-387/S-013, 015, & 027

Merck and Co., Inc.
Attention: Jeffrey R. Tucker, M.D.
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Tucker:

Please refer to your supplemental new drug applications dated April 1, 1999 (NDA 20-387/S-013), August 25, 1999 (NDA 20-387/S-015) and September 24, 2002 (NDA 20-387/S-027), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hyzaar (losartan potassium/hydrochlorothiazide) 50-12.5 and 100-25 mg Tablets.

We acknowledge receipt of your submissions dated September 16, 2003 (to NDA 20-387/S-013), September 2 and 16, 2003 (to NDA 20-387/S-015), and July 28 and September 2 and 16, 2003 (to NDA 20-387/S-027). Your submissions of September 16, 2003 constituted a complete response to our April 11, 2000 approvable letter (for NDA 20-387/S-013), our April 11, 2000 and May 20, 2003 approvable letters (for NDA 20-387/S-015), and our July 25, 2003 approvable letter (for NDA 20-387/S-027).

Electronic Final Printed Labeling (FPL) was received on September 16, 2003 for the following supplements:

NDA 20-387/S-027

This supplemental new drug application provides for a new use of Hyzaar (losartan potassium/hydrochlorothiazide) 50-12.5 and 100-25 mg Tablets in the treatment of hypertension. This fixed dose combination is not indicated for initial therapy of hypertension, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients. In addition, this supplement provides for revisions to the **DESCRIPTION, CLINICAL PHARMACOLOGY, ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION** sections of the labeling.

NDA 20-387/S-015

This "Changes Being Effected" supplement provides for the following labeling revisions:

1. Drug interaction information of losartan with rifampin, fluconazole, and erythromycin has been added to **CLINICAL PHARMACOLOGY,** *Drug Interactions* and **PRECAUTIONS,** *Drug Interactions*.
2. The subheading "*Use in the elderly*" has been changed to "*Geriatric Use*" under the **PRECAUTIONS** section. Additional information regarding geriatric use has also been added.

NDA 20-387/S-013

This "Changes Being Effected" supplement provides for the following labeling revisions:

1. Under **CLINICAL PHARMACOLOGY,** *Pharmacodynamics and Clinical Effects, Losartan Potassium*: the information on cough has been relocated to the **ADVERSE REACTIONS** section. In addition, the

following sentence has been added beneath the information on cough: "Cases of cough, including positive re-challenges, have been reported with the use of losartan in post-marketing experience."

2. **CLINICAL PHARMACOLOGY,** *Pharmacodynamics and Clinical Effects, Losartan Potassium*: In the fifth paragraph, the sentence "Black patients, however, had notably smaller responses to losartan monotherapy." has been replaced with "Losartan was effective in reducing blood pressure regardless of race, although the effect was somewhat less in black patients (usually a low-renin population)."

3. **ADVERSE REACTIONS,** *Post-Marketing Experience*: "Respiratory: Dry cough (see above) has been reported with losartan" has been added.

We have completed our review of these supplemental new drug applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted electronic final printed labeling (package inserts included in your submissions of September 16, 2003). Accordingly, these supplemental applications are approved effective on the date of this letter.

Please 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. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional materials and the package insert directly to:

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

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}

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

Enclosed Labeling Text

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

/s/

Doug Throckmorton
9/30/03 11:52:12 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-387/S-013, 015 & 027

Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-387/S-027

Merck & Co., Inc.
Attention: Jeffrey R. Tucker, M.D.
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Tucker:

Please refer to your supplemental new drug application dated September 24, 2002, submitted under Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hyzaar (losartan potassium/hydrochlorothiazide) 50-12.5 and 100-25 mg Tablets.

We acknowledge receipt of your submissions dated February 7, and 27, March 7 and 17 (two), April 22, and June 26, 2003.

This supplemental new drug application provides for a new use of Hyzaar (losartan potassium/hydrochlorothiazide) 50-12.5 and 100-25 mg Tablets for the initial treatment of hypertension so severe that the short-term risk of inadequate blood pressure control exceeds the excess risk of beginning the components, losartan and hydrochlorothiazide, together.

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 for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling (text for package insert).

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

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL, as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug 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 this product. Submit all proposed materials 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 insert 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 this 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.

This product may be considered 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) 594-5332

Sincerely,

{See appended electronic signature page}

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

Enclosure

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

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/s/

Doug Throckmorton
7/25/03 04:04:58 PM