DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-558/S-044
NDA 19-778/S-035

Merck & Co., Inc.
Attention: Jeffery 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 November 3, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prinivil (lisinopril) 2.5, 5, 10, 20 and 40 mg Tablets (NDA 19-558) and Prinzide (lisinopril/hydrochlorothiazide) 20/12.5 and 20/25 mg Tablets (NDA 19-778).

These "Changes Being Effected" supplemental new drug applications provide for changes to the **WARNINGS** section of labeling as follows:

1. Under **WARNINGS,** the **Angioedema** subsection was re-titled "**Head and Neck Angioedema**".

2. Following the **Head and Neck Angioedema** subsection and before the paragraph entitled "In large U.S. postmarketing study…" the following text has been added:

   Intestinal Angioedema: Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

3. Under **ADVERSE REACTIONS,** the following sentence has been added to the *Angioedema* subsection:

   In rare cases, intestinal angioedema has been reported with angiotensin converting enzyme inhibitors including lisinopril.

In addition we note the following revisions:

NDA 19-558
Under the HOW SUPPLIED section, the following discontinued packages have been deleted from the package insert:

NDC 0006-0015-28 unit dose packages of 100
NDC 0006-0015-31 unit of use bottles of 30
NDC 0006-0019-28 unit dose packages of 100
NDC 0006-0019-58 unit of use bottles of 100
NDC 0006-0019-94 unit of use bottles of 90
NDC 0006-0019-72 carton of 25 UNIBLISTER™ cards of 31 tablets each
NDC 0006-0106-28 unit dose packages of 100
NDC 0006-0106-31 unit of use bottles of 30
NDC 0006-0106-58 unit of use bottles of 90
NDC 0006-0106-94 unit of use bottles of 90
NDC 0006-0106-72 carton of 25 UNIBLSTER™ cards of 31 tablets each
NDC 0006-0207-28 unit dose packages of 100
NDC 0006-0207-31 unit of use bottles of 30
NDC 0006-0207-58 unit of use bottles of 100
NDC 0006-0207-94 unit of use bottles of 90
NDC 0006-0207-72 carton of 25 UNIBLISTER™ cards of 31 tablets each

We have completed our review of these supplemental new drug applications, as amended, and they are approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) dated on November 3, 2003.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
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:

Alisea Sermon, Pharm.D.
Regulatory Project Manager
(301) 594-5334

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

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

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