DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-558/S-046

Merck & Company, Inc.
Attention: Mr. Kenneth A. Kramer
Sumneytown Pike, P.O. Box 4, BLA-20
West Point, PA 19486

Dear Mr. Kramer:

Please refer to your supplemental new drug application dated April 15, 2005, 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.

This "Changes Being Effected" supplemental new drug application provide for revisions to the **WARNINGS/Head and Neck Angioedema** and **WARNINGS/Hepatic Failure** subsections based on post-marketing information.

This supplemental new drug application provides for electronic draft printed labeling with the following revisions:

1. Under the **WARNINGS/Head and Neck Angioedema** subsection the following revision has been proposed:

   From:

   In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal.

   To:

   Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient. Very rarely, fatalities have been reported due to angioedema associated with laryngeal edema or tongue edema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery.

2. Under the **WARNINGS/Hepatic Failure** subsection the following underlined revision has been proposed:

   Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice <u>or hepatitis</u> and progresses to fulminant hepatic necrosis, and (sometimes) death.

We have completed our review of this application, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

We also note the insertion of "Head and Neck" under the **INDICATIONS AND USAGE/Acute Myocardial Infarction** subsection to reflect subsection title in the **WARNINGS** section.

The final printed labeling (FPL) must be identical to the submitted electronic draft labeling dated April 15, 2005.

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 reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call please contact:

Alisea Sermon, Pharm.D.
Regulatory Project Manager
(301) 796-1144

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardiovascular and Renal 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/

Norman Stockbridge

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