DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-558/S-051 & S-052

Merck Research Laboratories
Attention: Mr. John Seneca
PO Box 1000, UG2C-50
North Wales, PA 19454-1099

Dear Mr. Seneca:

Please refer to your supplemental new drug applications dated February 11, 2008 (S-051) and April 28, 2008 (S-052), submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Prinivil (lisinopril) 5, 10, 20 & 40 mg Tablets.

We acknowledge receipt of your submissions dated March 14 and October 6, 2008 (S-051) and May 29 and October 6, 2008 (S-052).

These "Changes Being Effected" supplemental new drug applications provide for final electronic labeling with the following changes to the **ADVERSE REACTIONS** and **PRECAUTIONS** sections of the package insert.

S-051

1. Under **PRECAUTIONS**, Drug Interactions/*Non-steroidal Anti-inflammatory Drugs* subsection the following section has been changed from:

Non-steroidal Anti-inflammatory Agents: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of lisinopril may result in a further deterioration of renal function. These effects are usually reversible.

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors, including lisinopril. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of PRINIVIL alone were compared to PRINIVIL given concomitantly with indomethacin, the use of indomethacin was associated with a reduced antihypertensive effect, although the difference between the two regimens was not significant.

To:

Non-steroidal Anti-inflammatory Agents Including Selective Cyclooxygenase-2 (COX-2) Inhibitors: Reports suggest that NSAIDs including selective COX-2 inhibitors may diminish the antihypertensive effect of ACE inhibitors, including lisinopril. This interaction should be

given consideration in patients taking NSAIDs or selective COX-2 inhibitors concomitantly with ACE inhibitors.

In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of PRINIVIL alone were compared to PRINIVIL given concomitantly with indomethacin, the use of indomethacin was associated with a reduced antihypertensive effect, although the difference between the two regimens was not significant.

In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective COX-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible.

These interactions should be considered in patients taking NSAIDS including selective COX-2 inhibitors concomitantly with diuretics and angiotensin II antagonists or ACE inhibitors. Therefore, monitor effects on blood pressure and renal function when administering the combination, especially in the elderly.

2. Under the **ADVERSE REACTIONS**/*Skin* subsection, "cutaneous pseudolymphoma" has been added.

S-052

1. Under **ADVERSE REACTIONS**/*Endocrine* subsection, "syndrome of inappropriate antidiuretic hormone secretion (SIADH)" has been added.

We have completed our review of these applications, as amended, and they are approved, effective on the date of this letter, for use as recommended in the electronic draft labeling text. As soon as possible, but no later than 14 days from the date of this letter, please submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the submitted electronic labeling dated October 6, 2008. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

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
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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, please call:

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

Sincerely,

{See appended electronic signature page}

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

Norman Stockbridge

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