DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-558/S-050
19-778/S-040

Merck & Company, Inc.
Attention: Mr. Kenneth Kramer
PO Box 1000, UG2CD-48
North Wales, PA 19454-1099

Dear Mr. Kramer:

Please refer to your supplemental new drug applications dated September 18, 2006, 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/hctz) 20/12.5 and 20/25 Tablets (NDA 19-778).

These "Changes Being Effected" supplemental new drug applications provide for revisions to the **WARNINGS** and **PRECAUTIONS** sections of the labeling based on a recently published article regarding the use of ACE inhibitors during the first trimester of pregnancy.

These supplemental new drug applications provide for electronic draft labeling with the following revisions:

1. Under **WARNINGS**, *Fetal/Neonatal Morbidity and Mortality*, subsection the following paragraph has been added:

   In a published retrospective epidemiological study, infants whose mothers had taken an ACE inhibitor during their first trimester of pregnancy appeared to have an increased risk of major congenital malformations compared with infants whose mothers had not undergone first trimester exposure to ACE inhibitor drugs. The number of cases of birth defects is small and the findings of this study have not yet been repeated.

2. Under **PRECAUTIONS**/*Pregnancy* subsection the following text has been revised:

   From:

   Female patients of childbearing age should be told about the consequences of second and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

To:

Female patients of childbearing age should be told about the consequences of exposure to ACE inhibitors. These patients should be asked to report pregnancies to their physicians as soon as possible.

We have completed our review of these applications, and they are approved, effective on the date of this letter, for use as recommended in the electronic draft labeling text. 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 September 18, 2006. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

We also note the last revised labeling date has been updated to August 2006 for both Prinivil and Prinzide.

The final printed labeling (FPL) must be identical to the submitted labeling dated September 18, 2006.

Please submit an electronic version of the FPL 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. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved supplement NDA 19-558/S-050 and NDA 19-778/S-040**." Approval of these submissions by FDA is not required before the labeling is used.

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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