DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-364/S-036

Norvartis Pharmaceuticals Corporation
Attention: Ms. Donna Vivelo
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Ms. Vivelo:

Please refer to your supplemental new drug application dated August 22, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotrel (amlodipine besylate and benazepril HCl) 2.5/10, 5/10, 5/20 and 10/20 mg Capsules.

We also acknowledge your submission dated September 22, 2006.

This "Changes Being Effected" supplemental new drug application provides for revisions to the boxed Pregnancy Warning, **WARNINGS**, *Fetal/Neonatal Morbidity and Mortality* subsection, **PRECAUTIONS**, *Information for Patients* subsection and Pregnancy Category description based on a recently published article regarding the use of ACE inhibitors during the first trimester of pregnancy. This supplemental new drug application provides for electronic draft labeling with the following revisions:

1. Under **USE IN PREGNANCY (**boxed warning) the following text has been revised**:**

From:

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Lotrel should be discontinued as soon as possible. See **WARNINGS, Fetal/Neonatal Morbidity and Mortality.**

To:

USE IN PREGNANCY

When used in pregnancy, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Lotensin should be discontinued as soon as possible. See **WARNINGS, Fetal/Neonatal Morbidity and Mortality.**

2. Under **WARNINGS**, *Fetal/Neonatal Morbidity and Mortality* subsection the first and third paragraphs have been revised:

From:
ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When

pregnancy is detected, Lotrel should be discontinued as soon as possible.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of benazepril as soon as possible.

To:
ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, Lotensin should be discontinued as soon as possible and monitoring of the fetal development should be performed on a regular basis.

In addition, use of ACE inhibitors during the first trimester of pregnancy has been associated with a potentially increased risk of birth defects. In women planning to become pregnant, ACE inhibitors (including Lotensin) should not be used. Women of child-bearing age should be made aware of the potential risk and ACE inhibitors (including Lotensin) should only be given after careful counseling and consideration of individual risks and benefits.

3. Under **PRECAUTIONS**, the following **Pregnancy Category** statement has been revised:

From:
Pregnancy Categories C (first trimester) and D (second and third trimesters): See WARNINGS, Fetal/Neonatal Morbidity and Mortality

To:
Pregnancy Category D: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

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 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 August 22, 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.

The final printed labeling (FPL) must be identical to the submitted labeling dated September 22, 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 20-364/S-036**."
Approval of this submission 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:

Ms. Denise M. Hinton
Senior Regulatory Project Manager
(301) 796-1090

Sincerely,
{See appended electronic signature page}
Norman Stockbridge, M.D., Ph.D.
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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