DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-851/S-036
NDA 20-033/S-036

Novartis Pharmaceuticals Corporation
Attention: Ms. Lori Ann Bolognese
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Bolognese:

Please refer to your supplemental new drug applications dated November 30, 2007, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Lotensin (benazepril HCl) 5, 10, 20 and 40 mg Tablets (NDA 19-851) and Lotensin HCT (benazepril HCl and hydrochlorothiazide) 5/6.25, 10/12.5, 20/12.5 and 20/25 mg Tablets (NDA 20-033).

These supplemental new drug applications provide for electronic draft labeling with the following revisions to the **PRECAUTIONS** and **ADVERSE REACTIONS** sections of the labeling.

NDA 19-851

1. Under **PRECAUTIONS, Drug Interactions/Lithium** subsection, "including benazepril" has been added to the first sentence.

2. Under **PRECAUTIONS**, **Drug Interaction***s* subsection, the following **Anti-diabetics** description has been added:

   > **Anti-diabetics**: In rare cases, diabetic patients receiving an ACE inhibitor (including benazepril) concomitantly with insulin or oral anti-diabetics may develop hypoglycemia. Such patients should therefore be advised about the possibility of hypoglycemic reactions and should be monitored accordingly.

3. Under **PRECAUTIONS**, **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, the following sentence has been added to the paragraph:

   > No non-clinical studies have been conducted with the purpose of investigating potential juvenile toxicity of benazepril HCl.

4. Under **ADVERSE REACTIONS**, **Other** subsection, "frequent urination" has been added to the first sentence.

5. Under **ADVERSE REACTIONS**, **Other** subsection, the following sentence has been added:

   The following adverse events of unknown frequency have been reported during post-marketing use of benazepril: small bowel angioedema, anaphylactoid reactions, hyperkalemia, agranulocytosis, and neutropenia.

NDA 20-033

1. Under **PRECAUTIONS, Drug Interactions/Lithium** subsection, "including benazepril" has been added to the first sentence.

2. Under **PRECAUTIONS, Drug Interactions/Other** subsection, the subsection has been revised to read:

   Benazepril has been used concomitantly with beta-adrenergic-blocking agents, calcium-blocking agents, cimetidine, diuretics, digoxin, hydralazine, and naproxen without evidence of clinically important adverse interactions. Other ACE inhibitors have had less than additive effects with beta-adrenergic blockers, presumably because drugs of both classes lower blood pressure by inhibiting parts of the renin-angiotensin system.

   Interaction studies with warfarin and acenocoumarol have failed to identify any clinically important effects of benazepril on the serum concentrations or clinical effects of these anticoagulants.

   Insulin requirements in diabetic patients may be increased, decreased, or unchanged. In rare cases, diabetic patients receiving an ACE inhibitor (including benazepril) concomitantly with insulin or oral anti-diabetics may develop hypoglycemia. Such patients should therefore be advised about the possibility of hypoglycemic reactions, and should be monitored accordingly.

   Thiazides (including hydrochlorothiazide) may decrease arterial responsiveness to norepinephrine, but not enough to preclude effectiveness of the pressor agent for therapeutic use.

   Thiazides (including hydrochlorothiazide) may increase the responsiveness to tubocurarine.

   The diuretic, natriuretic, and antihypertensive effects of thiazide diuretics (including hydrochlorothiazide) may be reduced by concurrent administration of nonsteroidal anti-inflammatory agents.

   Coadministration of thiazide diuretics (including hydrochlorothiazide) may increase the risk of adverse effects caused by amantadine and may enhance the hyperglycemic effect of diazoxide.

   Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either

cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

Patients receiving hydrchlorothiazide concomitantly with caramazepine may develop hyponatremia. Such patients should therefore be advised about the possibility of hyponatremic reactions and should be monitored accordingly.

3. Under **ADVERSE REACTIONS, Drug Interactions** subsection, the following description has been added:

Unknown frequency: small bowel angioedma, anaphylactoid reactions, hyperkalemia, agranulocytosis, neutropenia.

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 November 30, 2007. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

The final printed labeling (FPL) must be identical to the submitted labeling dated November 30, 2007 with the following sentence omitted from the **PRECAUTIONS**, **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection (NDA 19-851/S-036).

[redacted]

Also, please correct the spelling of "carbamazepine" under the **PRECAUTIONS, Drug Interactions/Other** subsection and "angioedema" under the **ADVERSE REACTIONS**, **Drug Interaction/Unknown frequency** subsection.

We also note the last revised labeling date has been updated to November 2007 for both Lotensin and Lotensin HCT.

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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