DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 019851/S-043
NDA 020033/S-045

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Yifeng Jia, Ph.D.
Global Brand Regulatory Manager
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Jia:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received December 22, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lotensin (benazapril) 5 mg, 10 mg, 20 mg, and 40 mg Tablets (NDA 019851) and Lotensin HCT (benazapril/hydrochlorothiazide) 5/6.25 mg, 10/12.5 mg, 20/12.5 mg, and 25/25/mg Tablets (NDA 020033).

These "Prior Approval" supplemental new drug applications provide for labeling revised as follows:

For NDA 019851:

1. The Boxed Warning was changed:

> **WARNING: FETAL TOXICITY**
>
> - **When pregnancy is detected, discontinue Lotensin as soon as possible.**
> - **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. See WARNINGS: Fetal Toxicity**

2. Under **WARNINGS,** the section was changed from:

> **Fetal/Neonatal Morbidity and Mortality**
>
> 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.
>
> The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull

hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

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 childbearing 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.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, benazepril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Benazepril, which crosses the placenta, can theoretically be removed from the neonatal circulation by these means; there are occasional reports of benefit from these maneuvers with another ACE inhibitor, but experience is limited.

No teratogenic effects of Lotensin were seen in studies of pregnant rats, mice, and rabbits. On a mg/m2 basis, the doses used in these studies were 60 times (in rats), 9 times (in mice), and more than 0.8 times (in rabbits) the maximum recommended human dose (assuming a 50-kg woman). On a mg/kg basis these these multiples are 300 times (in rats), 90 times (in mice), and more than 3 times (in rabbits) the maximum recommended human dose.

To:

Fetal Toxicity
Pregnancy Category D
Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Lotensin as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most

epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.
In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Lotensin, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to Lotensin for hypotension, oliguria, and hyperkalemia. *[see Precautions, Pediatric Use]*

No teratogenic effects of Lotensin were seen in studies of pregnant rats, mice, and rabbits. On a mg/m2 basis, the doses used in these studies were 60 times (in rats), 9 times (in mice), and more than 0.8 times (in rabbits) the maximum recommended human dose (assuming a 50-kg woman). On a mg/kg basis these multiples are 300 times (in rats), 90 times (in mice), and more than 3 times (in rabbits) the maximum recommended human dose.

3. Under **PRECAUTIONS, Information for Patients,** the section was changed from:

Pregnancy: Female patients of childbearing age should be told about the consequences of exposure to ACE inhibitors Discuss other treatment options with women planning to become pregnant. 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 Lotensin during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

4. Under **PRECAUTIONS/Pediatric Use**, a new section was added:

Neonates with a history of *in utero* exposure to Lotensin:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

5. Throughout the label references to Fetal/Neonatal Morbidity and Mortality were deleted.

6. The revision date and version number were updated.

For NDA 020003:

1. The Boxed Warning was changed:

WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue Lotensin HCT as soon as possible.**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. See WARNINGS: Fetal Toxicity**

2. Under **WARNINGS,** the section was changed from:

Fetal/Neonatal Morbidity and Mortality

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 HCT should be discontinued as soon as possible and monitoring of the fetal development should be performed on a regular basis.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

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 HCT) should not be used. Women of childbearing 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.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, benazepril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Benazepril, which crosses the placenta, can theoretically be removed from the neonatal circulation by these means; there are occasional reports of benefit from these maneuvers with another ACE inhibitor, but experience is limited.

No teratogenic effects of Lotensin were seen in studies of pregnant rats, mice, and rabbits. On a mg/m2 basis, the doses used in these studies were 60 times (in rats), 9 times (in mice), and more than 0.8 times (in rabbits) the maximum recommended human dose (assuming a 50-kg woman). On a mg/kg basis these these multiples are 300 times (in rats), 90 times (in mice), and more than 3 times (in rabbits) the maximum recommended human dose.

To:

Fetal Toxicity
Pregnancy Category D
Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Lotensin HCT as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus. In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Lotensin HCT, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to Lotensin HCT for hypotension, oliguria, and hyperkalemia [see *Precautions, Pediatric Use*].

No teratogenic effects of benazapril were seen in studies of pregnant rats, mice, and rabbits. On a mg/m2 basis, the doses used in these studies were 60 times (in rats), 9 times (in mice), and more than 0.8 times (in rabbits) the maximum recommended human dose (assuming a 50-kg woman). On a mg/kg basis these these multiples are 300 times (in rats), 90 times (in mice), and more than 3 times

(in rabbits) the maximum recommended human dose. When hydrochlorothiazide was orally administered without benazepril to pregnant mice and rats during their respective periods of major organogenesis, at doses up to 3000 and 1000 mg/kg/day respectively, there was no evidence of harm to the fetus. Similarly, no teratogenic effects of benazepril were seen in studies of pregnant rats, mice, and rabbits; on a mg/kg basis, the doses used in these studies were 300 times (in rats), 90 times (in mice), and more than 3 times (in rabbits) the maximum recommended human dose.

3. Under **PRECAUTIONS, Information for Patients,** the section was changed from:

> **Pregnancy:** Female patients of childbearing age should be told about the consequences of exposure to ACE inhibitors Discuss other treatment options with women planning to become pregnant. 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 Lotensin HCT during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

4. Under **PRECAUTIONS/Pediatric Use**, a new section was added:

> Neonates with a history of *in utero* exposure to Lotensin HCT:
>
> If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

5. Throughout the label references to Fetal/Neonatal Morbidity and Mortality were deleted.

6. The revision date and version number were updated.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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:

Lori Anne Wachter, RN, BSN
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY R SOUTHWORTH
01/19/2012