



NDA 19-851/S-034
20-033/S-033

Novartis Pharmaceuticals, Inc
Attention: Mr. Carl Schlotfeldt
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Mr. Schlotfeldt:

Please refer to your supplemental new drug applications dated August 22, 2006, submitted under section 505(b) 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/hctz) 5mg/6.25mg, 10 mg/12.5 mg, 20mg/12.5 mg and 20/25 Tablets (NDA 20-033).

These “Changes Being Effected” supplemental new drug applications provide 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.

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

NDA 19-851

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, Lotensin 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 following 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, ACE inhibitors 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 subsection and heading has been changed:

a). Information for Patients/Pregnancy subsection:

From:

Pregnancy: 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:

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.

b). **Pregnancy Category** statement has been revised:

From:

Pregnancy Categories C (first trimester) and D (second and third trimesters)

To:

Pregnancy Category D

NDA 20-033

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, Lotensin HCT 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 HCT should be discontinued as soon as possible. See **WARNINGS, Fetal/Neonatal Morbidity and Mortality.**

2. Under **WARNINGS, Fetal/Neonatal Morbidity and Mortality** subsection the following 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, Lotensin HCT 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 HCT 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 HCT) should not be used. Women of child-bearing age should be made aware of the potential risk and ACE inhibitors (including Lotensin HCT) should only be given after careful counseling and consideration of individual risks and benefits.

3. Under **PRECAUTIONS**, the following subsection and heading has been changed:

a). **Information for Patients/Pregnancy** subsection:

From:

Pregnancy: 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:

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.

b). **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 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 August 22, 2006. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

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

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 19-851/S-034 and NDA 20-033/S-033.**"

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

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/s/

Norman Stockbridge
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