



NDA 19-777/S-052
19-888/S-043

AstraZeneca Pharmaceuticals LP
Attention: Ms. Paula Clark
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Dear Ms. Clark:

Please refer to your supplemental new drug applications dated January 29, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zestril® (lisinopril) 2.5, 5, 10, 20, 30 and 40 mg Tablets (NDA 19-777) and Zestoretic® (lisinopril/hctz) 10/12.5, 20/12.5 and 20/25 mg Tablets (NDA 19-888).

We also acknowledge receipt of your submission dated February 28, 2007 (NDA 19-777).

These 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 during pregnancy. 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 January 29, 2007. 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 January 2007 for both Zestril® and Zestoretic®.

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) 796-114

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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
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/s/

Norman Stockbridge
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