



NDA 19-777/S-053  
19-888/S-044

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 April 5, 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/S-053) and Zestoretic® (lisinopril/hctz) 10/12.5, 20/12.5 and 20/25 mg Tablets (NDA 19-888/S-044).

These supplemental new drug applications provide for editorial revisions to the **WARNINGS/Anaphylactoid Reactions During Membrane Exposure** section, information regarding nitritoid reactions with injectable gold to the **PRECAUTIONS/Drug Interactions** and an update to add cutaneous pseudolymphoma to the **ADVERSE REACTIONS/Skin** subsection.

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

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1. Under the **WARNINGS/ Anaphylactoid Reactions During Membrane Exposure**, “must” has been added to the following paragraph.

Sudden and potentially life threatening anaphylactoid reactions have been reported in some patients dialyzed with high-flux membranes (e.g., AN69®\*) and treated concomitantly with an ACE inhibitor. In such patients, dialysis must be stopped immediately, and aggressive therapy for anaphylactoid reactions must be initiated. Symptoms have not been relieved by antihistamines in these situations. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

2. Under the **PRECAUTIONS/Drug Interactions** subsection, the following paragraph has been added:

**Gold:** Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including ZESTRIL.

3. Under the **ADVERSE REACTIONS/Skin** subsection, cutaneous pseudolymphoma has been added.

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4. Under the **WARNINGS/Anaphylactoid Reactions During Membrane Exposure**, “must” has been added to the following paragraph.

Thiazide-containing combination products are not recommended in patients with severe renal dysfunction. Sudden and potentially life-threatening anaphylactoid reactions have been reported in some patients dialyzed with high-flux membranes (eg, AN69®\*) and treated concomitantly with an ACE inhibitor. In such patients, dialysis must be stopped immediately, and aggressive therapy for anaphylactoid reactions must be initiated. Symptoms have not been relieved by antihistamines in these situations. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

5. Under the **PRECAUTIONS/Drug Interactions** subsection, the following paragraph has been added:

**Gold** - Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including ZESTORETIC.

6. Under the **ADVERSE REACTIONS/Skin** subsection, cutaneous pseudolymphoma has been added.

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(1)] 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 April 5, 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 March 2007 for both Zestril® and Zestoretic®.

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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

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/

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Norman Stockbridge  
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