DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-777/S-050
NDA 19-888/S-041

AstraZeneca Pharmaceuticals LP
Attention: Ms. Judy W. Firor
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Dear Ms. Firor:

Please refer to your supplemental new drug applications dated December 28, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zestril® (lisinopril) 2.5, 5, 10, 20, 30 & 40 mg Tablets (NDA 19-777) and Zestoretic® (lisinopril/hctz) 20/12.5, 20/25 and 10/12.5 mg Tablets (NDA 19-888).

These "Changes Being Effected" supplemental new drug applications provide for revisions to the **PRECAUTIONS** and **ADVERSE REACTIONS** sections to update information for Hypoglycemia and Hyperkalemia based on post-marketing information and literature review.

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

NDA 19-777

1. Under **PRECAUTIONS/Hyperkalemia** subsection

From:

Risk factors for the development of hyperkalemia include renal insuffiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containg salt substitutes, which should be used cautiously, if at all, with ZESTRIL. (See Drug Interactons).

To:

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes. Hyperkalemia can cause serious, sometimes fatal, arrhythmias. ZESTRIL should be used cautiously, if at all, with these agents and with frequent monitoring of serum potassium. (See Drug Interactions.)

2. Under **PRECAUTIONS**, the following subsections have been added:

   Hypoglycemia: Diabetic patients treated with oral antidiabetic agents or insulin starting an ACE inhibitor should be told to closely monitor for hypoglycemia, especially during the first month of combined use. (See PRECAUTIONS, Drug Interactions.)

   Antidiabetics: Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment. In diabetic patients treated with oral antidiabetic agents or insulin, glycemic control should be closely monitored for hypoglycemia, especially during the first month of treatment with an ACE inhibitor.

3. Under **PRECAUTIONS**, "eplerenone" has been added under the **Agents Increasing serum Potassium** subsection.

4. Under **ADVERSE REACTIONS**, the following text has been added under the **Metabolic** subsection:

   Cases of hypoglycemia in diabetic patients on oral antidiabetic agents or insulin have been reported in post-marketing experience (See PRECAUTIONS, Drug Interactions).

NDA 19-888

1. Under **PRECAUTIONS/Hyperkalemia** subsection:

From:

> Risk factors for the development of hyperkalemia include renal insuffiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containg salt substitutes, which should be used cautiously, if at all, with ZESTORETIC. (See Drug Interactons).

To:

> Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes. Hyperkalemia can cause serious, sometimes fatal, arrhythmias. ZESTORETIC should be used cautiously, if at all, with these agents and with frequent monitoring of serum potassium. (See Drug Interactions.)

2. Under **PRECAUTIONS**, "eplerenone" has been added under the **Agents Increasing serum Potassium** subsection.

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 final printed labeling (FPL) submitted on December 29, 2005.

If you issue a letter communicating important information about these drug products (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, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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 contact:

Alisea Sermon, Pharm.D.
Regulatory Project Manager
(301) 796-1144

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardio-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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