



NDA 20-387/S-038

Merck Research Laboratories  
Attention: Kenneth Kramer, RPh  
Associate Director, Regulatory Affairs Domestic  
P.O. Box 4, BLA-20  
West Point, PA 19486

Dear Mr. Kramer:

Please refer to your supplemental new drug application dated 25 October 2005, received 26 October 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HYZAAR (losartan potassium hydrochlorothiazide) 50-12.5, 100-12.5, and 100-25 mg Tablets.

This "Changes Being Effected in 30 days" supplemental new drug application provides for:

1. Under CLINICAL PHARMACOLOGY, *Pharmacokinetics, General, Losartan Potassium*, the Pediatric section was revised from:

Losartan pharmacokinetics have not been investigated in patients <18 years of age

To:

Losartan pharmacokinetics have been investigated in patients 6-16 years (See PRECAUTIONS, *Pediatric Use*).

2. Under Precautions-*Drug Interaction, Losartan Potassium* section, the following third paragraph was deleted:

As with other antihypertensive agents, the antihypertensive effect of losartan may be blunted by the non-steroidal anti-inflammatory drug indomethacin.

The following paragraphs were added:

*Non-Steroidal Anti-Inflammatory Agents including Cyclooxygenase-2 Inhibitors*: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs (NSAIDS) including those that selectively inhibit cyclooxygenase-2 inhibitors (COX-2 inhibitors), the co-administration of angiotensin II receptor antagonists including losartan, may result in a further deterioration of renal function. These effects are usually reversible.

Reports suggest that NSAIDS including selective COX-2 inhibitors may diminish the antihypertensive effect of angiotensin II receptor antagonists, including losartan. This interaction should be given consideration in patients taking NSAIDS including selective COX-2 inhibitors concomitantly with angiotensin II receptor antagonists.

3. Under Precautions, *Non-Steroidal Anti-Inflammatory Drugs* was revised to I include the following verbage: "including Selective Cyclooxygenase-2 Inhibitors" after all *Non-steroidal Anti-Inflammatory Drugs*.

4. Under Precautions, the *Pediatric Use* section revised to:

Safety and Effectiveness of HYZAAR in pediatric patients have not been established.

5. Minor editorial revisions were noted:

- a. Hyphen was added between “ACE” and “inhibitor”
- b. Label component number was revised from 9573626 to 9573627
- c. Comma replaced colon after “See WARNINGS” in Box Warning
- d. Issue date updated to September 2005
- e. Copyright date updated to 2004

We completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the electronic final printed labeling (eFPL) submitted on 30 September 2005.

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  
WO 22, Room 4447  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call:

Cheryl Ann Borden, MSN, RN, CCRN, CCNS  
Regulatory Health Project Manager  
(301) 796.1046.

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

Encl: Label

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/s/

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Norman Stockbridge  
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