DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-901/S-034

King Pharmaceuticals, Inc.
Attention: Mr. Dean R. Cirotta
501 Fifth Street
Bristol, TN 37620

Dear Mr. Cirotta:

Please refer to your supplemental new drug application dated August 16, 2001, received submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Altace (ramipril) 1.25, 2.5, 5 and 10 mg Capsules.

This "Changes Being Effected" supplemental new drug application provides for final printed labeling with the following revisions:

1. The first paragraph under the CONTRAINDICATIONS section has been changed from:

   ALTACE is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor.

   To:

   ALTACE is contraindicated in patients who are hypersensitive to this product or any other angiotensin converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor.

2. The first two sentences under the WARNINGS/Neutropenia/Agranulocytosis subsection have been changed from:

   Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients, but more frequently in patients with renal impairment, especially if they also have collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of ramipril are insufficient to show that ramipril does not cause agranulocytosis at similar rates.

To:

As with other ACE inhibitors, rarely, a mild – in isolated cases severe – reduction in the red blood cell count and hemoglobin content, white blood cell or patelet count may develop. In isolated cases, agranulocytosis, pancyotpenia, and bone marrow depression may occur. Hematological reactions to ACE inhibitors are more likely to occur in patients with collagen vascular disease (e.g., systemic lupus erythematosus, scleroderma) and renal impairment.

3. The following sentence has been added to the end of the PRECAUTIONS/Impaired Liver Function subsection:

However, since the renin-angiotensin system maybe activated in patients with severe liver cirrhosis and/or ascites, particular caution should be exercised in treating these patients.

4. The following sub-subsection has been added to the PRECAUTIONS/Drug Interactions subsection:

With nonsteroidal anti-inflammatory agents: Rarely, concomitant treatment with ACE inhibitors and nonsteroidal anti-inflammatory agents have been associated with worsening of renal failure and an increase in serum potassium.

5. The following have been added to the ADVERSE REACTIONS/Dermatologic subsection:

… pemphigoid, Stevens-Johnson syndrome, toxic epidermal necrolysis, and onycholysis…

The word, “not” is misspelled in the second paragraph of the OVERDOSAGE section. Please make the correction at the time of the next printing.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling included in your August 16, 2001 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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, call Ms. Zelda McDonald, Regulatory Health Project Manager, at (301) 594-5333.

Sincerely,

{See appended electronic signature page}

Douglas C.Throckmorton M.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/

Doug Throckmorton
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