DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-901/S-046

King Pharmaceuticals, Inc.
Attention: Ms. Felicia Bullock
501 Fifth Street
Bristol, Tennessee 37620

Dear Ms. Bullock:

Please refer to your supplemental new drug application dated August 24, 2004, 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" special supplemental new drug application provides for the inclusion of additional safety information in the Altace® prescribing information regarding hepatobiliary adverse events and hypoglycemia.

This supplemental new drug application provides for the following revisions:

1. Under the **WARNINGS/Hepatic Failure** section

   From:

   "Rarely, ACE inhibitors, have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death."

   To:

   "Rarely, ACE inhibitors, including Altace, have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death."

2. Under the **ADVERSE REACTIONS/Gastrointestinal** subsection: hepatic failure, and jaundice have been added and the word "hepatitis" has been relocated.

   From:

   "Pancreatitis, abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, hepatitis, increased salivation and taste disturbance."

   To:

   "Hepatic failure, hepatitis, jaundice, pancreatitis, abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, increased salivation and taste disturbance.

3. Under the **ADVERSE REACTIONS/Other** subsection, "**(see PRECAUTIONS, Drug Interactions)**" has been removed.

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

> "Post-Marketing Experience: In addition to adverse events reported from clinical trials, there have been rare reports of hypoglycemia reported during ALTACE therapy when given to patients concomitantly taking oral hypoglycemia agents or insulin. The casual relationship is unknown."

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling dated August 24, 2004.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-901/S-046." Approval of this submission by FDA is not required before the labeling is used.

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, 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 call:

Alisea Sermon, Pharm.D.
Regulatory Project Manager
(301) 594-5334

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting 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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