DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

SEP - 7 2000

Norman T. Miller
Senior Director, Regulatory Affairs
King Pharmaceuticals, Inc.
501 5th Street
Bristol, TN 37620

RE: **NDA #19-901**
Altace (ramipril) Capsules
MACMIS ID# 9002

Dear Mr. Miller:

As part of its routine monitoring program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware of a promotional labeling piece for Altace (ramipril) Capsules, disseminated by Monarch Pharmaceuticals, a division of King Pharmaceuticals, Inc. Your announcement letter, identified as 1-1015-1, submitted under cover of Form FDA 2253, violates the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. The announcement letter promotes Altace for unapproved uses, contains unsubstantiated superiority claims, and lacks fair balance. Our specific objections follow:

Unapproved Uses

The announcement letter states:

> "Treatment with ramipril showed significant improvement for...
> - ...the rates of stroke, MI, revascularization procedures, cardiac arrest, heart failure, and death from either cardiovascular causes or other causes...
> - ...fewer diabetes-related complications...
> - ...fewer new cases of diabetes...
> - ...reduction in atherosclerosis progression."

This announcement letter suggests Altace is indicated for reducing morbidity and mortality in high risk patients with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus one other cardiovascular risk factor. However, Altace is not approved for these uses. The *Indications and Usage* section of the

approved product labeling (PI) for Altace states that it is indicated for the treatment of hypertension and heart failure post-myocardial infarction. Therefore, the announcement letter promotes Altace for unapproved uses, in violation of the Act.

We note that you present a disclaimer, in small size type at the end of the letter that "Ramipril (ALTACE) does not have an approved indication for the prevention of cardiovascular death, myocardial infarction, and stroke...." However, the inclusion of this disclaimer does not adequately correct the implications made by claims presented in this announcement letter.

Unsubstantiated Superiority Claims

Claims in this announcement letter imply that Altace is unique and superior to all other ACE inhibitors. For example, you claim:

- ...results of ramipril treatment...are not replicated by all other ACE inhibitors and thus do not reflect a class activity
- Altace (ramipril) has unique properties related to lipid solubility, half-life, tissue specificity, ACE affinity, and binding
- This provides a unique triphasic elimination process resulting in an extended terminal elimination half-life ranging from 3 to 50 times as long as other marketed ACE inhibitors

These implications of clinical superiority are not based on substantial evidence (i.e., adequate and well controlled, head-to-head clinical trials) comparing Altace to all other ACE inhibitors. Furthermore, it is misleading to use pharmacokinetic data to imply clinical relevance or superiority. Therefore, the implication that Altace is superior to other ACE inhibitors is misleading because it is not supported by substantial evidence.

Lack of Fair Balance

Promotional materials must present information relating to contraindications, precautions, and side effects in a manner reasonably comparable to the presentation of information on the effectiveness of the drug. Your letter contains efficacy claims but fails to provide any information on the risks associated with Altace. The PI contains a boxed warning on risk of injury or death to the developing fetus when used in pregnancy during the second and third trimesters, as well as other warnings, precautions, and serious adverse reactions associated with the use of Altace. Therefore, the announcement letter lacks fair balance because it fails to include any information on risks associated with the use of Altace.

Requested Action

In order to address these objections, you should immediately cease distribution of this announcement letter and all other promotional materials for Altace that contain the same or similar claims or presentations. You should respond in writing by September 21, 2000, with your intent and plans to comply with this request. Your response should include a list of materials discontinued, and the date on which these materials were discontinued.

If you have any further questions, please direct them to me by facsimile at 301-594-6771 or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857.

We remind you that only written communications are considered official. In all future correspondence regarding this particular matter please refer to MACMIS ID #9002 in addition to the NDA number.

Sincerely,

Andrew S.T. Haffer, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

Monarch Pharmaceuticals®
355 Beecham Street | Bristol, Tennessee 37620 | ph 800-776-3637 | www.monarchpharm.com
A Division of King Pharmaceuticals, Inc.

Dear Colleague:

On January 20, the *New England Journal of Medicine* published a major article entitled "Effects of an Angiotensin-Coverting-Enzyme Inhibitor, Ramipril, on Cardiovascular Events in High-Risk Patients." This article reports the results of the Heart Outcomes Prevention Evaluation (HOPE) Study.

The HOPE Study was halted six months early of its scheduled 5-year duration by the Data Safety Monitoring Board on ethical grounds—because of clear evidence of beneficial effects with ramipril*. The *NEJM* posted this report on the Internet on 11/10/99, prior to publication, "because of the potential therapeutic implications."

The HOPE Study was a double-blind, placebo-controlled, multicenter trial involving 9541 patients with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus one other cardiovascular risk factor. These patients were randomized to receive the long-acting ACE inhibitor, ALTACE® (ramipril) 10 mg or matching placebo.

HOPE was designed to learn if ramipril would reduce morbidity and mortality in patients at high risk for cardiovascular events—beyond its established indications of hypertension treatment and heart failure management following myocardial infarction. For this reason, patients with uncontrolled hypertension were excluded from the study, as were patients with heart failure or those known to have a low ejection fraction.

Treatment with ramipril showed significant improvement for all primary and secondary study endpoints. These included the rates of stroke, MI, revascularization procedures, cardiac arrest, heart failure, and death from either cardiovascular causes or other causes. Among patients who entered the study with diabetes, those treated with ramipril had significantly fewer diabetes-related complications. For all other patients, significantly fewer new cases of diabetes occurred in the ramipril-treated patients.

A substudy of 732 patients in the HOPE Study was conducted utilizing carotid ultrasound to measure atherosclerosis in carotid arteries. This substudy showed a significant reduction in atherosclerosis progression for those treated with ramipril versus placebo.

The HOPE Study stands in sharp contrast to the earlier, well-controlled study of a different ACE inhibitor, the Quinapril Ischemic Event Trial (QUIET). That placebo-controlled trial followed 1750 patients for three years. It showed no significant effect on cardiac events or on the progression of atherosclerosis in patients with coronary artery disease. **The strikingly different outcomes of the two studies strongly suggest results of ramipril treatment in the HOPE Study are not replicated by all other ACE inhibitors and thus do not reflect a class activity.**

Continued...

ALTACE® (ramipril*) has unique properties related to lipid solubility, half-life, tissue specificity, ACE affinity, and binding. This provides a unique triphasic elimination process resulting in an extended terminal elimination half-life ranging from 3 to 50 times as long as other marketed ACE inhibitors. Whether these unique pharmacological properties account for the remarkable results of the HOPE Study is not known.

For a copy of the full HOPE Study, complete the form below and FAX it to (888) 296-8173. To reach a member of the Monarch Professional Information Services Department with a question or for further information about ALTACE® (ramipril), please call (800) 776-3637.

Sincerely,

R. Henry Richards, M.D.

Henry Richards, MD
Medical Director

*Ramipril (ALTACE®) does not have an approved indication for the prevention of cardiovascular death, myocardial infarction, and stroke as studied and demonstrated in the HOPE Study. Please consult complete product information before prescribing.

Please PRINT or TYPE and FAX entire sheet to 888-296-8173.

NAME

ADDRESS

STREET

CITY STATE ZIP

PHONE

AREA CODE

Please provide me with the following materials (initial the appropriate box(es) and sign below).

☐ **A reprint of the *NEJM* article reporting the HOPE Study**

☐ **Clinical starter supplies of ALTACE®** (ramipril)

signature required