CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-901/S046

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-901/S046

Trade Name: Altace

Generic Name: Ramipril

Sponsor: King Pharmaceutical

Approval Date: November 15, 2004

Indications: Hypertension

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-901/S046

APPROVAL LETTER

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
11/15/04 11:04:31 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-901/S046

LABELING

Prescribing Information as of September 2004.

ALTACE® Capsules
(ramipril)

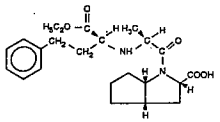
USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ALTACE® should be discontinued as soon as possible. See **WARNINGS: Fetal/neonatal morbidity and mortality.**

DESCRIPTION

Ramipril is a 2-aza-bicyclo [3.3.0]-octane-3-carboxylic acid derivative. It is a white, crystalline substance soluble in polar organic solvents and buffered aqueous solutions. Ramipril melts between 105°C and 112°C.

The CAS Registry Number is 87333-19-5. Ramipril's chemical name is (2S,3aS,6aS)-1[(S)-N-[(S)-1-Carboxy-3-phenylpropyl] alanyl] octahydrocyclopenta [b]pyrrole-2-carboxylic acid, 1-ethyl ester. Its structural formula is:



Its empiric formula is $C_{23}H_{32}N_2O_5$, and its molecular weight is 416.5.

Ramiprilat, the diacid metabolite of ramipril, is a non-sulfhydryl angiotensin converting enzyme inhibitor. Ramipril is converted to ramiprilat by hepatic cleavage of the ester group.

ALTACE (ramipril) is supplied as hard shell capsules for oral administration containing 1.25 mg, 2.5 mg, 5 mg, and 10 mg of ramipril. The inactive ingredients present are pregelatinized starch NF, gelatin, and titanium dioxide. The 1.25 mg capsule shell contains yellow iron oxide, the 2.5 mg capsule shell contains D&C yellow #10 and FD&C red #40, the 5 mg capsule shell contains FD&C blue #1 and FD&C red #40, and the 10 mg capsule shell contains FD&C blue #1.

CLINICAL PHARMACOLOGY

Mechanism of Action

Ramipril and ramiprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. In hypertensive patients with normal renal function treated with ALTACE alone for up to 56 weeks, approximately 4% of patients during the trial had an abnormally high serum potassium and an increase from baseline greater than 0.75 mEq/L, and none of the patients had an abnormally low potassium and a decrease from baseline greater than 0.75 mEq/L. In the same study, approximately 2% of patients treated with ALTACE and hydrochlorothiazide for up to 56 weeks had abnormally high potassium values and an increase from baseline of 0.75 mEq/L or greater, and approximately 2% had abnormally low values and decreases from baseline of 0.75 mEq/L or greater. (See **PRECAUTIONS**.) Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

The effect of ramipril on hypertension appears to result at least in part from inhibition of both tissue and circulating ACE activity, thereby reducing angiotensin II formation in tissue and plasma.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of ALTACE remains to be elucidated.

While the mechanism through which ALTACE lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, ALTACE has an antihypertensive effect even in patients with low-renin hypertension. Although ALTACE was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to monotherapy than non-black patients.

Pharmacokinetics and Metabolism

Following oral administration of ALTACE, peak plasma concentrations of ramipril are reached within one hour. The extent of absorption is at least 50–60% and is not significantly influenced by the presence of food in the GI tract, although the rate of absorption is reduced.

In a trial in which subjects received ALTACE capsules or the contents of identical capsules dissolved in water, dissolved in apple juice, or suspended in apple sauce, serum ramiprilat levels were essentially unrelated to the use or nonuse of the concomitant liquid or food.

Cleavage of the ester group (primarily in the liver) converts ramipril to its active diacid metabolite, ramiprilat. Peak plasma concentrations of ramiprilat are reached 2–4 hours after drug intake. The serum protein binding of ramipril is about 73% and that of ramiprilat about 56%; in vitro, these percentages are independent of concentration over the range of 0.01 to 10µg/ml.

Ramipril is almost completely metabolized to ramiprilat, which has about 6 times the ACE inhibitory activity of ramipril, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat, all of which are inactive. After oral administration of ramipril, about 60% of the parent drug and its metabolites is eliminated in the urine, and about 40% is found in the feces. Drug recovered in the feces may represent both biliary excretion of metabolites and/or unabsorbed drug. However the proportion of a dose eliminated by the bile has not been determined. Less than 2% of the administered dose is recovered in urine as unchanged ramipril.

Blood concentrations of ramipril and ramiprilat increase with increased dose, but are not strictly dose-proportional. The 24-hour AUC for ramiprilat, however, is dose-proportional over the 2.5–20 mg dose range. The absolute bioavailabilities of ramipril and ramiprilat were 28% and 44%, respectively, when 5 mg of oral ramipril was compared with the same dose of ramipril given intravenously.

Plasma concentrations of ramiprilat decline in a triphasic manner (initial rapid decline, apparent elimination phase, terminal elimination phase). The initial rapid decline, which represents distribution of the drug into a large peripheral compartment and subsequent binding to both plasma and tissue ACE, has a half-life of 2–4 hours. Because of its potent binding to ACE and slow dissociation from the enzyme, ramiprilat shows two elimination phases. The apparent elimination phase corresponds to the clearance of free ramiprilat and has a half-life of 9–18 hours. The terminal elimination phase has a prolonged half-life (>50 hours) and probably represents the binding/dissociation kinetics of the ramiprilat/ACE complex. It does not contribute to the accumulation of the drug. After multiple daily doses of ramipril 6–10 mg, the half-life of ramiprilat concentrations within the therapeutic range was 13–17 hours.

After once-daily dosing, steady-state plasma concentrations of ramiprilat are reached by the fourth dose. Steady-state concentrations of ramiprilat are somewhat higher than those seen after the first dose of ALTACE, especially at low doses (2.5 mg), but the difference is clinically insignificant.

In patients with creatinine clearance less than 40 ml/min/1.73m², peak levels of ramiprilat are approximately doubled, and trough levels may be as much as quintupled. In multiple-dose regimens, the total exposure to ramiprilat (AUC) in these patients is 3–4 times as large as it is in patients with normal renal function who receive similar doses.

The urinary excretion of ramipril, ramiprilat, and their metabolites is reduced in patients with impaired renal function. Compared to normal subjects, patients with creatinine clearance less than 40 ml/min/1.73m² had higher peak and trough ramiprilat levels and slightly longer times to peak concentrations. (See **DOSAGE AND ADMINISTRATION**.)

In patients with impaired liver function, the metabolism of ramipril to ramiprilat appears to be slowed, possibly because of diminished activity of hepatic esterases, and plasma ramipril levels in these patients are increased about 3-fold. Peak concentrations of ramiprilat in these patients, however, are not different from those seen in subjects with normal hepatic function, and the effect of a given dose on plasma ACE activity does not vary with hepatic function.

Pharmacodynamics

Single doses of ramipril of 2.5–20 mg produce approximately 60–80% inhibition of ACE activity 4 hours after dosing with approximately 40–60% inhibition after 24 hours. Multiple oral doses of ramipril of 2.0 mg or more cause plasma ACE activity to fall by more than 90% 4 hours after dosing, with over 80% inhibition of ACE activity remaining 24 hours after dosing. The more prolonged effect of even small multiple doses presumably reflects saturation of ACE binding sites by ramiprilat and relatively slow release from those sites.

Pharmacodynamics and Clinical Effects

Reduction in Risk of Myocardial Infarction, Stroke, and Death from Cardiovascular Causes

The Heart Outcomes Prevention Evaluation study (HOPE study) was a large, multicenter, randomized, placebo controlled, 2x2 factorial design, double-blind study conducted in 9,541 patients (4,645 on ALTACE) who were 55 years or older and considered at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that was accompanied by at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria). Patients were either normotensive or under treatment with other antihypertensive agents. Patients were excluded if they had clinical heart failure or were known to have a low ejection fraction (<0.40). This study was designed to examine the long-term (mean of five years) effects of ALTACE (10 mg orally once a day) on the combined endpoint of myocardial infarction, stroke or death from cardiovascular causes.

The HOPE study results showed that ALTACE (10 mg/day) significantly reduced the rate of myocardial infarction, stroke or death from cardiovascular causes (651/4645 vs. 826/4652, relative risk 0.78), as well as the rates of the 3 components of the combined endpoint.

Outcome	Altace (N=4645) no. (%)	Placebo (N=4652) no. (%)	Relative Risk (95% CI) P value
Combined End-point (MI, stroke, or death from CV cause)	651 (14.0%)	826 (17.8%)	0.78 (0.70–0.86), P=0.0001
Component End-point Death from Cardiovascular Causes	262 (6.1%)	377 (8.1%)	0.74 (0.64–0.87), P=0.0002
Myocardial Infarction	459 (9.9%)	570 (12.3%)	0.80 (0.70–0.90), P=0.0003
Stroke	156 (3.4%)	225 (4.9%)	0.69 (0.56–0.84), P=0.0002
Overall Mortality (Death from any Cause)	482 (10.4%)	569 (12.2%)	0.84 (0.75–0.95), P=0.005

This effect was evident after about one year of treatment.

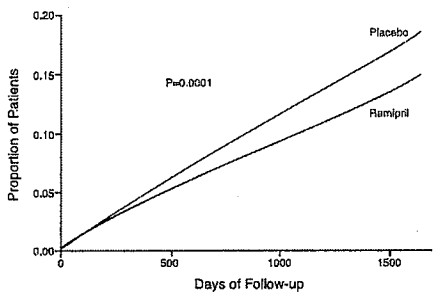


Figure 1: Kaplan-Meier Estimates of the composite outcome of MI, Stroke, or Death from CV causes in the Ramipril Group and the Placebo Group. The relative risk of the composite outcomes in the Ramipril Group as compared with the Placebo Group was 0.78% (95% confidence interval, 0.70–0.86).

Ramipril was effective in different demographic subgroups, (i.e., gender, age), subgroups defined by underlying disease (e.g., cardiovascular disease, hypertension), and subgroups defined by concomitant medication. There were insufficient data to determine whether or not ramipril was equally effective in ethnic subgroups.

This study was designed with a prespecified substudy in diabetics with at least one other cardiovascular risk factor. Effects of ramipril on the combined endpoint and its components were similar in diabetics (n=3,577) to those in the overall study population.

Outcome	Altace (N=1808) no. (%)	Placebo (N=1769) no. (%)	Relative Risk Reduction (95% CI)
Combined End-point (MI, stroke, or death from CV cause)	277 (15.3%)	351 (19.8%)	0.25 (0.12–0.36), P=0.0004
Component End-point Death from Cardiovascular Causes	112 (6.2%)	172 (9.7%)	0.37 (0.21–0.51), P=0.0001
Myocardial Infarction	185 (10.2%)	229 (12.9%)	0.22 (0.06–0.36), P=0.01
Stroke	76 (4.2%)	108 (6.1%)	0.33 (0.10–0.50), P=0.007

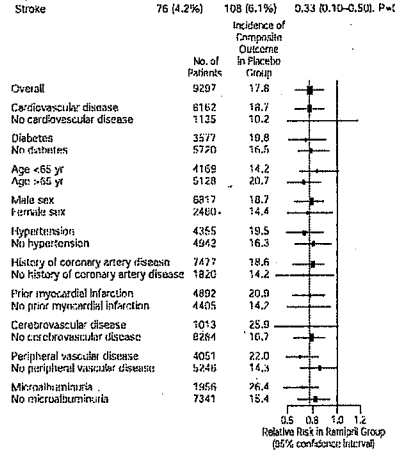


Figure 2. The Beneficial Effect of Treatment with Ramipril on the Composite Outcome of Myocardial Infarction, Stroke, or Death from Cardiovascular Causes Overall and in Various Subgroups. Cerebrovascular disease was defined as stroke or transient ischemic attacks. The size of each symbol is proportional to the number of patients in each group. The dashed line indicates overall relative risk.

The benefits of Altace were observed among patients who were taking aspirin or other anti-platelet agents, beta-blockers, and lipid-lowering agents as well as diuretics and calcium channel blockers.

Hypertension

Administration of ALTACE to patients with mild to moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt- and/or volume-depleted. (See **WARNINGS.**) Use of ALTACE in combination with thiazide diuretics gives a blood pressure lowering effect greater than that seen with either agent alone.

In single-dose studies, doses of 5–20 mg of ALTACE lowered blood pressure within 1–2 hours, with peak reductions achieved 3–6 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. In longer term (4–12 weeks) controlled studies, once-daily doses of 2.5–10 mg were similar in their effect, lowering supine or standing systolic and diastolic blood pressures 24 hours after dosing by about 6/4 mm Hg more than placebo. In comparisons of peak vs. trough effect, the trough effect represented about 50–60% of the peak response. In a titration study comparing divided (bid) vs. qd treatment, the divided regimen was superior, indicating that for some patients the antihypertensive effect with once-daily dosing is not adequately maintained. (See **DOSAGE AND ADMINISTRATION.**)

In most trials, the antihypertensive effect of ALTACE increased during the first several weeks of repeated measurements. The antihypertensive effect of ALTACE has been shown to continue during long-term therapy for at least 2 years. Abrupt withdrawal of ALTACE has not resulted in a rapid increase in blood pressure.

ALTACE has been compared with other ACE inhibitors, beta-blockers, and thiazide diuretics. It was approximately as effective as other ACE inhibitors and as atenolol. In both caucasians and blacks, hydrochlorothiazide (25 or 50 mg) was significantly more effective than ramipril.

Except for thiazides, no formal interaction studies of ramipril with other antihypertensive agents have been carried out. Limited experience in controlled and uncontrolled trials combining ramipril with a calcium channel blocker, a loop diuretic, or triple therapy (beta-blocker, vasodilator, and a diuretic) indicate no unusual drug-drug interactions. Other ACE inhibitors have had less than additive effects with beta adrenergic blockers, presumably because both drugs lower blood pressure by inhibiting parts of the renin-angiotensin system.

ALTACE was less effective in blacks than in caucasians. The effectiveness of ALTACE was not influenced by age, sex, or weight.

In a baseline controlled study of 10 patients with mild essential hypertension, blood pressure reduction was accompanied by a 15% increase in renal blood flow. In healthy volunteers, glomerular filtration rate was unchanged.

Heart Failure Post Myocardial Infarction

ALTACE was studied in the Acute Infarction Ramipril Efficacy (AIRE) trial. This was a multinational (mainly European) 161-center, 2006-patient, double-blind, randomized, parallel-group study comparing ALTACE to placebo in stable patients, 2–9 days after an acute myocardial infarction (MI), who had shown clinical signs of congestive heart failure (CHF) at any time after the MI. Patients in severe (NYHA class IV) heart failure, patients with unstable angina, patients with heart failure of congenital or valvular etiology, and patients with contraindications to ACE inhibitors were all excluded. The majority of patients had received thrombolytic therapy at the time of the index infarction, and the average time between infarction and initiation of treatment was 5 days.

Patients randomized to ramipril treatment were given an initial dose of 2.5 mg twice daily. If the initial regimen caused undue hypotension, the dose was reduced to 1.25 mg, but in either event doses were titrated upward (as tolerated) to a target regimen (achieved in 77% of patients randomized to ramipril) of 5 mg twice daily. Patients were then followed for an average of 15 months (range 6–46).

The use of ALTACE was associated with a 27% reduction (p=0.002). In the risk of death from any cause: about 90% of the deaths that occurred were cardiovascular, mainly sudden death. The risks of progression to severe heart failure and of CHF-related hospitalization were also reduced, by 23% (p=0.017) and 26% (p=0.011), respectively. The benefits of ALTACE therapy were seen in both genders, and they were not affected by the exact timing of the initiation of therapy, but older patients may have had a greater benefit than those under 65. The benefits were seen in patients on, and not on, various concomitant medications; at the time of randomization these included aspirin (about 80% of patients), diuretics (about 60%), organic nitrates (about 55%), beta-blockers (about 20%), calcium channel blockers (about 15%), and digoxin (about 12%).

INDICATIONS AND USAGE

Reduction in Risk of Myocardial Infarction, Stroke, and Death from Cardiovascular Causes

Altace is indicated in patients 55 years or older at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that is accompanied by at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria), to reduce the risk of myocardial infarction, stroke, or death from cardiovascular causes. Altace can be used in addition to other needed treatment (such as antihypertensive, antiplatelet or lipid-lowering therapy).

Hypertension

ALTACE is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ALTACE, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that ALTACE does not have a similar risk. (See **WARNINGS.**)

In considering use of ALTACE, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients. (See **WARNINGS, Angioedema.**)

Heart Failure Post Myocardial Infarction

Ramipril is indicated in stable patients who have demonstrated clinical signs of congestive heart failure within the first few days after sustaining acute myocardial infarction. Administration of ramipril to such patients has been shown to decrease the risk of death (principally cardiovascular death) and to decrease the risks of failure-related hospitalization and progression to severe/resistant heart failure. (See **CLINICAL PHARMACOLOGY, Heart Failure Post Myocardial Infarction** for details and limitations of the survival trial.)

CONTRAINDICATIONS

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).

WARNINGS

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including ALTACE) may be subject to a variety of adverse reactions, some of them serious.

Head and Neck Angioedema

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. (See also **CONTRAINDICATIONS.**)

Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin converting enzyme inhibitors. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ALTACE should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1,000 (0.3 ml to 0.5 ml) should be promptly administered.** (See **ADVERSE REACTIONS.**)

Intestinal Angioedema

Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

In a large U.S. postmarketing study, angioedema (defined as reports of angio, face, larynx, tongue, or throat edema) was reported in 3/1523 (0.20%) of black patients and in 8/6580 (0.09%) of white patients. These rates were not different statistically.

Anaphylactoid reactions during desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid reactions during membrane exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Hypotension

ALTACE can cause symptomatic hypotension, after either the initial dose or a later dose when the dosage has been increased. Like other ACE inhibitors, ramipril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with ALTACE.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ALTACE therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of ramipril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with intravenous infusion of physiological saline. ALTACE treatment usually can be continued following restoration of blood pressure and volume.

ALTACE® Capsules
(ramipril)
Prescribing Information as of September 2004.

Hepatic Failure

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. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Neutropenia/Agranulocytosis

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 platelet count may develop. In isolated cases, agranulocytosis, pancytopenia, 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. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ALTACE as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, ALTACE should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. ALTACE which crosses the placenta can be removed from the neonatal circulation by these means, but limited experience has not shown that such removal is central to the treatment of these infants.

No teratogenic effects of ALTACE were seen in studies of pregnant rats, rabbits, and cynomolgus monkeys. On a body surface area basis, the doses used were up to approximately 400 times (in rats and monkeys) and 2 times (in rabbits) the recommended human dose.

PRECAUTIONS

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ALTACE, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ALTACE and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy. Some hypertensive patients who had no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ALTACE has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ALTACE and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. (See **DOSAGE AND ADMINISTRATION.**)

Hyperkalemia: In clinical trials, hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1% of hypertensive patients receiving ALTACE (ramipril). In most cases, these were isolated values, which resolved despite continued therapy. None of these patients was discontinued from the trials because of hyperkalemia. 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, which should be used cautiously, if at all, with ALTACE. (See **Drug Interactions.**)

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Impaired Liver Function: Since ramipril is primarily metabolized by hepatic esterases to its active moiety, ramiprilat, patients with impaired liver function could develop markedly elevated plasma levels of ramipril. No formal pharmacokinetic studies have been carried out in hypertensive patients with impaired liver function. However, since the renin-angiotensin system may be activated in patients with severe liver cirrhosis and/or ascites, particular caution should be exercised in treating these patients.

Surgery/Anesthesia: In patients undergoing surgery or during anesthesia with agents that produce hypotension, ramipril may block angiotensin II formation that would otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, or tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported. Patients should be told that if syncope occurs, ALTACE should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to promptly report any indication of infection (e.g., sore throat, fever), which could be a sign of neutropenia.

Drug Interactions

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.

With diuretics: Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ALTACE. The possibility of hypotensive effects with ALTACE can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ALTACE. If this is not possible, the starting dose should be reduced. (See **DOSAGE AND ADMINISTRATION.**)

With potassium supplements and potassium-sparing diuretics: ALTACE can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

With lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other: Neither ALTACE nor its metabolites have been found to interact with food, digoxin, antacid, furosemide, cimetidine, indomethacin, and simvastatin. The combination of ALTACE and propranolol showed no adverse effects on dynamic parameters (blood pressure and heart rate). The co-administration of ALTACE and warfarin did not adversely affect the anticoagulant effects of the latter drug. Additionally, co-administration of ALTACE with phenprocoumon did not affect minimum phenprocoumon levels or interfere with the subjects' state of anti-coagulation.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a tumorigenic effect was found when ramipril was given by gavage to rats for up to 24 months at doses of up to 500 mg/kg/day or to mice for up to 18 months at doses of up to 1000 mg/kg/day. (For either species, these doses are about 200 times the maximum recommended human dose when compared on the basis of body surface area.) No mutagenic activity was detected in the Ames test in bacteria, the micronucleus test in mice, unscheduled DNA synthesis in a human cell line, or a forward gene-mutation assay in a Chinese hamster ovary cell line. Several metabolites and degradation products of ramipril were also negative in the Ames test. A study in rats with dosages as great as 500 mg/kg/day did not produce adverse effects on fertility.

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters). See **WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

Nursing Mothers

Ingestion of single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, women receiving ALTACE should not breast feed.

Geriatric Use

Of the total number of patients who received ramipril in US clinical studies of ALTACE 11.0% were 65 and over while 0.2% were 75 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

One pharmacokinetic study conducted in hospitalized elderly patients indicated that peak ramiprilat levels and area under the plasma concentration time curve (AUC) for ramiprilat are higher in older patients.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Irreversible kidney damage has been observed in very young rats given a single dose of ramipril.

ADVERSE REACTIONS

Hypertension

ALTACE has been evaluated for safety in over 4,000 patients with hypertension; of these, 1,230 patients were studied in US controlled trials, and 1,107 were studied in foreign controlled trials. Almost 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was similar in ALTACE and placebo patients. The most frequent clinical side effects (possibly or probably related to study drug) reported by patients receiving ALTACE in US placebo-controlled trials were: headache (5.4%), "dizziness" (2.2%) and fatigue or asthenia (2.0%), but only the last was more common in ALTACE patients than in patients given placebo. Generally, the side effects were mild and transient, and there was no relation to total dosage within the range of 1.25 to 20 mg. Discontinuation of therapy because of a side effect was required in approximately 3% of US patients treated with ALTACE. The most common reasons for discontinuation were: cough (1.0%), "dizziness" (0.5%), and impotence (0.4%).

Of observed side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with ALTACE, only asthenia (fatigue) was more common on Altace than placebo (2% vs. 1%).

PATIENTS IN US PLACEBO CONTROLLED STUDIES

	ALTACE (n=551)		Placebo (n=286)	
	n	%	n	%
Asthenia (Fatigue)	13	2	2	1

In placebo-controlled trials, there was also an excess of upper respiratory infection and flu syndrome in the ramipril group, not attributed at that time to ramipril. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ramipril patients, with about 4% of patients requiring discontinuation of treatment.

Heart Failure Post Myocardial Infarction

Adverse reactions (except laboratory abnormalities) considered possibly/probably related to study drug that occurred in more than one percent of patients and more frequently on ramipril are shown below. The incidences represent the experiences from the AIRE study. The follow-up time was between 6 and 46 months for this study.

Percentage of Patients with Adverse Events Possibly/ Probably Related to Study Drug

Placebo-Controlled (AIRE) Mortality Study

Adverse Event	Ramipril (n=1004)	Placebo (n=982)
Hypotension	11	5
Cough Increased	9	4
Dizziness	4	3
Angina Pectoris	3	2
Nausea	2	1
Postural Hypotension	2	1
Syncope	2	1
Vomiting	2	0.5
Vertigo	2	0.7
Abnormal Kidney Function	1	0.5
Diarrhea	1	0.4

HOPE Study:

Safety data in the HOPE trial were collected as reasons for discontinuation or temporary interruption of treatment. The incidence of cough was similar to that seen in the AIRE trial. The rate of angioedema was the same as in previous clinical trials (see **WARNINGS**).

	RAMIPRIL (N=4645)	PLACEBO (N=4652)
	%	%
Discontinuation at any time	34	32
Permanent discontinuation	29	28
Reasons for stopping Cough	7	2
Hypotension or Dizziness	1.9	1.5
Angioedema	0.3	0.1

Other adverse experiences reported in controlled clinical trials (in less than 1% of ramipril patients), or rarer events seen in postmarketing experience, include the following (in some, a causal relationship to drug use is uncertain):

Body As a Whole: Anaphylactoid reactions. (See **WARNINGS.**)

Cardiovascular: Symptomatic hypotension (reported in 0.5% of patients in US trials) (See **WARNINGS** and **PRECAUTIONS**), syncope and palpitations.

Hematologic: Pancytopenia, hemolytic anemia and thrombocytopenia.

Renal: Some hypertensive patients with no apparent pre-existing renal disease have developed minor, usually transient, increases in blood urea nitrogen and serum creatinine when taking ALTACE, particularly when ALTACE was given concomitantly with a diuretic. (See **WARNINGS.**) Acute renal failure.

Angioneurotic Edema: Angioneurotic edema has been reported in 0.3% of patients in US clinical trials. (See **WARNINGS.**)

Gastrointestinal: 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.

Dermatologic: Apparent hypersensitivity reactions (manifested by urticaria, pruritus, or rash, with or without fever), photosensitivity, purpura, onycholysis, pemphigus, pemphigoid, erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome.

Neurologic and Psychiatric: Anxiety, amnesia, convulsions, depression, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, somnolence, tinnitus, tremor, vertigo, and vision disturbances.

Miscellaneous: As with other ACE inhibitors, a symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, vasculitis, eosinophilia, photosensitivity, rash and other dermatologic manifestations. Additionally, as with other ACE inhibitors, eosinophilic pneumonitis has been reported.

Fetal/Neonatal Morbidity and Mortality. See **WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

Other: arthralgia, arthritis, dyspnea, edema, epistaxis, impotence, increased sweating, malaise, myalgia, and weight gain.

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 hypoglycemic agents or insulin. The causal relationship is unknown.

Clinical Laboratory Test Findings:

Creatinine and Blood Urea Nitrogen: Increases in creatinine levels occurred in 1.2% of patients receiving ALTACE alone, and in 1.5% of patients receiving ALTACE and a diuretic. Increases in blood urea nitrogen levels occurred in 0.5% of patients receiving ALTACE alone and in 3% of patients receiving ALTACE with a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis. (See **WARNINGS** and **PRECAUTIONS.**) Since ramipril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently. (See **WARNINGS** and **PRECAUTIONS.**)

Hemoglobin and Hematocrit: Decreases in hemoglobin or hematocrit (a low value and a decrease of 5 g/dl or 5% respectively) were rare, occurring in 0.4% of patients receiving ALTACE alone and in 1.5% of patients receiving ALTACE plus a diuretic. No US patients discontinued treatment because of decreases in hemoglobin or hematocrit.

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with ALTACE administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have cases of hyponatremia and scattered incidents of leukopenia, eosinophilia, and proteinuria. In US trials, less than 0.2% of patients discontinued treatment for laboratory abnormalities; all of these were cases of proteinuria or abnormal liver-function tests.

OVERDOSAGE

Single oral doses in rats and mice of 10–11 g/kg resulted in significant lethality. In dogs, oral doses as high as 1 g/kg induced only mild gastrointestinal distress. Limited data on human overdosage are available. The most likely clinical manifestations would be symptoms attributable to hypotension.

Laboratory determinations of serum levels of ramipril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of ramipril overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of ramipril and its metabolites. Similarly, it is not known which, if any, of these substances can be usefully removed from the body by hemodialysis.

Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of ramipril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of ramipril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat ramipril overdose by infusion of normal saline solution.

DOSAGE AND ADMINISTRATION

Blood pressure decreases associated with any dose of ALTACE depend, in part, on the presence or absence of volume depletion (e.g., past and current diuretic use) or the presence or absence of renal artery stenosis. If such circumstances are suspected to be present, the initial starting dose should be 1.25 mg once daily.

Reduction in Risk of Myocardial Infarction, Stroke, and Death from Cardiovascular Causes

ALTACE should be given at an initial dose of 2.5 mg, once a day for 1 week, 5 mg, once a day for the next 3 weeks, and then increased as tolerated, to a maintenance dose of 10 mg, once a day. If the patient is hypertensive or recently post myocardial infarction, it can also be given as a divided dose.

Hypertension

The recommended initial dose for patients not receiving a diuretic is 2.5 mg once a day. Dosage should be adjusted according to the blood pressure response. The usual maintenance dosage range is 2.5 to 20 mg per day administered as a single dose or in two equally divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice daily administration should be considered. If blood pressure is not controlled with ALTACE alone, a diuretic can be added.

Heart Failure Post Myocardial Infarction

For the treatment of post-infarction patients who have shown signs of congestive failure, the recommended starting dose of ALTACE is 2.5 mg twice daily (5 mg per day). A patient who becomes hypotensive at this dose may be switched to 1.25 mg twice daily, and after one week at the starting dose, patients should then be titrated (if tolerated) toward a target dose of 5 mg twice daily, with dosage increases being about 3 weeks apart.

After the initial dose of ALTACE, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See **WARNINGS** and **PRECAUTIONS, Drug Interactions.**) If possible, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of ALTACE does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

The ALTACE Capsule is usually swallowed whole. The ALTACE Capsule can also be opened and the contents sprinkled on a small amount (about 4 oz.) of apple sauce or mixed in 4 oz. (120 ml) of water or apple juice. To be sure that ramipril is not lost when such a mixture is used, the mixture should be consumed in its entirety. The described mixtures can be pre-prepared and stored for up to 24 hours at room temperature or up to 48 hours under refrigeration.

Concomitant administration of ALTACE with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics can lead to increases of serum potassium. (See **PRECAUTIONS.**)

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of ALTACE. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued two to three days prior to beginning therapy with ALTACE. (See **WARNINGS.**) Then, if blood pressure is not controlled with ALTACE alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 1.25 mg ALTACE should be used to avoid excess hypotension.

Dosage Adjustment in Renal Impairment

In patients with creatinine clearance <40 ml/min/1.73m² (serum creatinine approximately >2.5 mg/dl) doses only 25% of those normally used should be expected to induce full therapeutic levels of ramiprilat. (See **CLINICAL PHARMACOLOGY.**)

Hypertension: For patients with hypertension and renal impairment, the recommended initial dose is 1.25 mg ALTACE once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 5 mg.

Heart Failure Post Myocardial Infarction: For patients with heart failure and renal impairment, the recommended initial dose is 1.25 mg ALTACE once daily. The dose may be increased to 1.25 mg b.i.d. and up to a maximum dose of 2.5 mg b.i.d. depending upon clinical response and tolerability.

HOW SUPPLIED

ALTACE is available in potencies of 1.25 mg, 2.5 mg, 5 mg, and 10 mg in hard gelatin capsules.

ALTACE 1.25 mg capsules are supplied as yellow, hard gelatin capsules in bottles of 100 (NDC 61570-110-01), and Unit Dose packs of 100 (NDC 61570-110-56).

ALTACE 2.5 mg capsules are supplied as orange, hard gelatin capsules in bottles of 100 (NDC 61570-111-01), 500 (NDC 61570-111-05), 1000 (NDC 61570-111-10) and Unit Dose packs of 100 (NDC 61570-111-56), and Bulk pack of 5000's (NDC 61570-111-50).

ALTACE 5 mg capsules are supplied as red, hard gelatin capsules in bottles of 100 (NDC 61570-112-01), 500 (NDC 61570-112-05), 1000 (NDC 61570-112-10) and Unit Dose packs of 100 (NDC 61570-112-56), and Bulk pack of 5000's (NDC 61570-112-50).

ALTACE 10 mg capsules are supplied as Process Blue, hard gelatin capsules in bottles of 100 (NDC 61570-120-01), 500 (NDC 61570-120-05), 1000 (NDC 61570-120-10).

Dispense in well-closed container with safety closure.

Store at controlled room temperature (59° to 86°F).

Rx only.

Monarch Pharmaceuticals®

Distributed by: Monarch Pharmaceuticals, Inc., Bristol, TN 37620
(A wholly owned subsidiary of King Pharmaceuticals, Inc.)
Manufactured by: King Pharmaceuticals, Inc., Bristol, TN 37620

Prescribing Information as of September 2004. 3000246-D

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-901/S046

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

RHPM Review of FPL
NDA 19-901/S-046

Date of Submissions:	December 21, 2004
Draft Labeling Approved:	November 15, 2004
FPL Submitted:	December 22, 2004
Date of Review:	May 23, 2005
Sponsor Name:	King Pharmaceuticals
Product(s) Name:	Altace (ramipril) Capsules

Evaluation:

This Changes Being Effected supplemental application provides for the inclusion of additional safety information in the Altace prescribing information regarding hepatobiliary adverse events and hypoglycemia.

The sponsor has proposed the following changes:

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."

Recommendation:

The FPL is identical to the draft labeling that was approved on November 15, 2005. An acknowledge and retain letter will be issued for the above supplemental new drug application.

Alisea Sermon, Pharm.D.

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/s/

Alisea Sermon
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CSO

RHPM Review of Draft Labeling
NDA 19-901/S-046

Date of Submissions:	August 24, 2004
Draft Labeling Submitted:	August 25, 2004
Date of Review:	October 12, 2004
Sponsor Name:	King Pharmaceuticals
Product(s) Name:	Altace (ramipril) Capsules

Evaluation:

This Changes Being Effected supplemental application provides for the inclusion of additional safety information in the Altace prescribing information regarding hepatobiliary adverse events and hypoglycemia.

The sponsor has proposed the following changes:

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   "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."

Recommendation:

In accordance with 21 CFR 314.70 (c)(2)(i), changes may be made to add or strengthen a contraindication, warning, precaution or adverse reaction section of labeling. In our letter dated March, 15, 2004 the Division requested removal of a proposed [redacted] statement under the **PRECAUTIONS** section (S-040) because the data did not support the proposed change. The sponsor has now submitted additional rationale and safety reports to support the above changes; in addition, the sponsor has requested a teleconference with the Division if we are not in agreement with the proposed language, specifically [redacted] wording. b(4)

Alisea Sermon, Pharm.D. b(4)

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/s/

Alisea Sermon
11/15/04 10:37:00 AM
CSO

Alisea Sermon
11/15/04 10:46:15 AM
CSO

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 A. Bullock
501 Fifth Street
Bristol, TN 37620

Dear Ms. Bullock:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Altace® (ramipril) 1.25, 2.5, 5, and 10 mg Capsules
NDA Number:	19-901
Supplement number:	046
Date of supplement:	August 24, 2004
Date of receipt:	August 25, 2004

This supplemental application, submitted as "Supplement - Changes Being Effected" proposes additional safety information in the Altace® prescribing information regarding hepatobiliary adverse events and hypoglycemia.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 24, 2004, in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call:

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

Sincerely,

{See appended electronic signature page}

Edward Fromm
Acting Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
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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, TN 37620

Dear Ms. Bullock:

We acknowledge receipt of your December 21, 2004 submission containing final printed labeling in response to our November 15, 2004 letter approving your new drug application (NDA) for Altace (ramipril) 1.25, 2.5, 5 and 10 mg Capsules.

We have reviewed the labeling that you submitted in accordance with our November 15, 2004 letter, and we find it acceptable.

If you have any questions, please contact:

Alisea Sermon, Pharm.D.
Regulatory Health 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

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/s/

Norman Stockbridge
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