



NDA 19901/S-055

SUPPLEMENT APPROVAL

King Pharmaceuticals, Inc
Attention: Karen Baker
Senior Manager, Regulatory Affairs
501 Fifth Street
Bristol, TN 37620

Dear Ms. Baker:

Please refer to your Supplemental New Drug Application (sNDA) dated August 6, 2009, received August 7, 2009 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Altace (ramipril) 1.25 mg, 2.5 mg, 5 mg and 10 mg capsules.

This Prior Approval supplemental new drug application provides for revision to the labeling of Altace with the following content changes:

The entire label has been revised to conform with PLR format.

There were several editorial changes throughout the label to change to active voice.

The **BOXED WARNING** was revised:

From

<p style="text-align: center;">WARNING: USE IN PREGNANCY</p> <ul style="list-style-type: none">• When used in pregnancy during the second and third trimesters, angiotensin converting enzyme (ACE) inhibitors can cause injury and even death to the developing fetus.• When pregnancy is detected, ALTACE® should be discontinued as soon as possible (5.6).
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To

<p style="text-align: center;">WARNING: AVOID USE IN PREGNANCY <i>See full prescribing information for complete boxed warning</i> When used in pregnancy, ACE inhibitors can cause injury and death to the developing fetus. When pregnancy is detected, discontinue ALTACE® as soon as possible (5.6).</p>
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In the **DOSAGE AND ADMINISTRATION** section:

From

Renal Impairment

Evaluation of the hypertensive patient should always include assessment of renal function. The usual regimens of therapy with ALTACE may be followed if the patient's creatinine clearance is ≥ 40 mL/min/1.73 m² (serum creatinine approximately ≤ 2.5 mg/dL). In patients with creatinine clearance < 40 mL/min/1.73 m², 25% of the usual dose of ramipril is expected to produce full therapeutic levels of ramiprilat [*see Clinical Pharmacology (12.3.4)*].

To

Renal Impairment

Establish baseline renal function in patients initiating ALTACE. Usual regimens of therapy with ALTACE may be followed in patients with estimated creatinine clearance > 40 mL/min. However, in patients with worse impairment, 25% of the usual dose of ramipril is expected to produce full therapeutic levels of ramiprilat [*see Use in Specific Population (8.6)*].

In the **DOSAGE FORMS AND STRENGTHS** section:

From

...hard shell capsules...

To

...hard gelatin capsules...

In the **WARNINGS AND PRECAUTIONS** section:

From

5.2 Hepatic Failure and Impaired Liver Function

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.

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-aldosterone system may be activated in patients with severe liver cirrhosis and/or ascites, particular caution should be exercised in treating these patients.

To

5.2 Hepatic Failure and Impaired Liver Function

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. Discontinue ALTACE if patient develops jaundice or marked elevations of hepatic enzymes.

As 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.

And

Deleted under Section 5.4 *Neutropenia and Agranulocytosis*

In using ALTACE, consideration should be given to the fact that another ACE 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.

And

From

5.5 Hypotension

General Considerations

ALTACE can cause symptomatic hypotension, after either the initial dose or a later dose when the dosage has been increased. Like other ACE inhibitors, ALTACE, 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.

If excessive 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.

Heart Failure Post-Myocardial Infarction

In patients with heart failure post-myocardial infarction 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 2–3 days prior to beginning therapy with ALTACE. 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 excessive hypotension.

To

5.5 Hypotension

General Considerations

ALTACE can cause symptomatic hypotension, after either the initial dose or a later dose when the dosage has been increased. Like other ACE inhibitors, ALTACE, 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. Correct volume- and salt-depletion before initiating therapy with ALTACE.

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

Heart Failure Post-Myocardial Infarction

In patients with heart failure post-myocardial infarction who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of ALTACE. If the initial dose of 2.5 mg ALTACE cannot be tolerated, use an initial dose of 1.25 mg ALTACE to avoid excessive hypotension. Consider reducing the dose of concomitant diuretic to decrease the incidence of hypotension.

And

Added

5.7 Dual Blockade of the Renin-Angiotensin-Aldosterone System

Telmisartan

The ONTARGET trial enrolled 25,620 patients >55 years old with atherosclerotic disease or diabetes with end-organ damage, randomized them to telmisartan only, ramipril only, or the combination, and followed them for a median of 56 months. Patients receiving the combination of telmisartan and ramipril did not obtain any benefit in the composite endpoint of cardiovascular death, MI, stroke and heart failure hospitalization compared to monotherapy, but experienced an increased incidence of clinically important renal dysfunction (death, doubling of serum creatinine, or dialysis) compared with groups receiving telmisartan alone or ramipril alone. Concomitant use of telmisartan and ramipril is not recommended.

In the **DRUG INTERACTIONS**, *Other Antihypertensive Agents* section:

Added

In a large-scale, long-term clinical efficacy study, the combination of telmisartan and ramipril resulted in an increased incidence of clinically important renal dysfunction (death, doubling of serum creatinine, dialysis) compared with groups receiving either drug alone. Therefore, concomitant use of telmisartan and ramipril is not recommended. [see Dual Blockade of the Renin-Angiotensin-Aldosterone System (5.7)].

In the **USE IN SPECIFIC POPULATIONS** section:

From

8.1 Pregnancy

Pregnancy Category C and D

There are no adequate and well-controlled studies with ALTACE in pregnant women. ALTACE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. [see *Warnings and Precautions* (5.6)].

8.3 Nursing Mothers

Ingestion of a 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 a single dose, women receiving ALTACE should not breast feed.

To

8.1 Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters) [see *Warnings and Precautions* (5.6)].

8.3 Nursing Mothers

Ingestion of a 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 a single dose, do not use ALTACE in nursing mothers.

And

Added

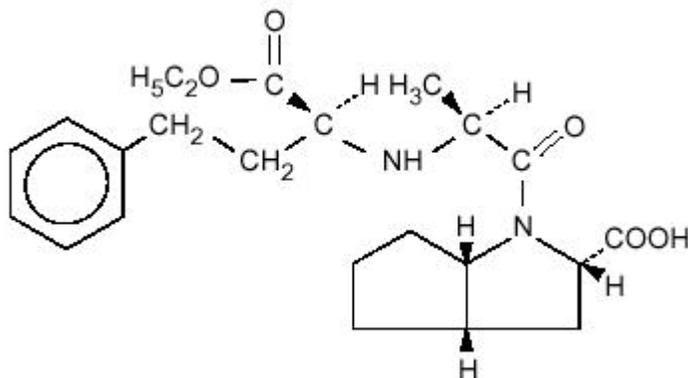
8.6 Renal Impairment

A single-dose pharmacokinetic study was conducted in hypertensive patients with varying degrees of renal impairment who received a single 10 mg dose of ramipril. Patients were stratified into four groups based on initial estimates of creatinine clearance: normal (>80 mL/min), mild impairment (40-80 mL/min), moderate impairment (15-40 mL/min), and severe impairment (<15 mL/min). On average, the AUC_{0-24h} for

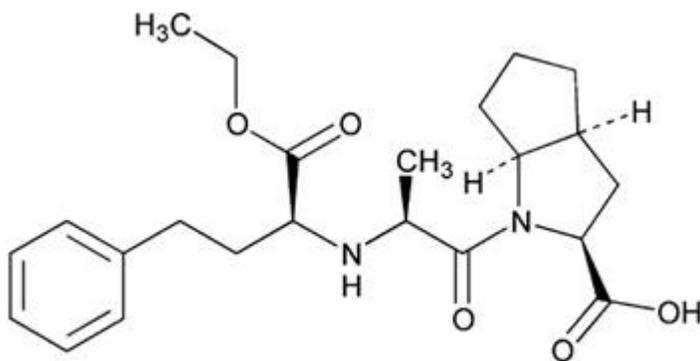
ramiprilat was approximately 1.7-fold higher, 3.0-fold higher, and 3.2-fold higher in the groups with mild, moderate, and severe renal impairment, respectively, compared to the group with normal renal function. Overall, the results suggest that the starting dose of ramipril should be adjusted downward in patients with moderate-to-severe renal impairment.

In the **DESCRIPTION** section the structural formula was revised:

From



To



In the **CLINICAL STUDIES**, *14.1 Hypertension* section:

Added underlined sections

In single-dose studies, doses of 5 mg–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 mg–10 mg were similar in their effect, lowering supine or standing systolic and diastolic blood pressures 24 hours after dosing by about 6/4 mmHg 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.

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. ALTACE 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.

In the **HOW SUPPLIED/STORAGE AND HANDLING** section:

The table headings were re-ordered

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

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(1)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

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 Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY R SOUTHWORTH
10/21/2010