



NDA 019901/S-059

SUPPLEMENT APPROVAL

King Pharmaceuticals, LLC
Attention: Sheetal Alur
Sr. Manager Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Ms. Alur:

Please refer to your Supplemental New Drug Application (sNDA) dated and received March 29, 2012, submitted under section 505(b)(1) 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 labeling revised as follows:

In Highlights:

1. The boxed warning was changed:

<p>WARNING: FETAL TOXICITY</p> <p><i>See full prescribing information for complete boxed warning.</i></p> <ul style="list-style-type: none"> • When pregnancy is detected, discontinue ALTACE as soon as possible (5.6) • Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus (5.6)

2. Under Recent Major Changes, the following was added/~~deleted~~:

----- RECENT MAJOR CHANGES -----	
Boxed Warning: Fetal Toxicity	03/2012
Warnings and Precautions: Fetal Toxicity (5.6)	03/2012

WARNINGS AND PRECAUTIONS

- ~~Dual Blockade of the Renin-Angiotensin-Aldosterone System: Telmisartan (5.7)~~ 10/2010

3. In ADVERSE REACTIONS, the following was added/~~deleted~~:

To report SUSPECTED ADVERSE REACTIONS, contact **King Pharmaceuticals, Inc.** at 1-800-546-4905/438-1985 or DSP@kingpharm.com or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

In Full Prescribing Information:

4. The boxed warning was changed:

<p style="text-align: center;">WARNING: FETAL TOXICITY</p> <ul style="list-style-type: none">• When pregnancy is detected, discontinue ALTACE as soon as possible. (5.6)• Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.6)

5. Under **WARNINGS AND PRECAUTIONS**, the section was changed from:

5.6 Fetal/Neonatal Morbidity and Mortality

Angiotensin converting enzyme 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, discontinue ACE inhibitors 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 caused by the ACE inhibitor exposure.

In a published retrospective epidemiological study, infants whose mothers had taken an ACE inhibitor during their first trimester of pregnancy appeared to have an increased risk of major congenital malformations compared with infants whose mothers had not undergone first trimester exposure to ACE inhibitor drugs. The number of cases of birth defects is small and the findings of this study have not yet been confirmed.

Rarely (probably less than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin-aldosterone system will be found. In these rare cases, inform mothers about the potential hazards to their fetuses, and perform serial ultrasound examinations to assess the intraamniotic environment.

If oligohydramnios is observed, discontinue ALTACE unless it is considered life-saving for the mother. Contraction stress testing, a nonstress test, or biophysical profiling 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. Closely observe infants with histories of *in utero* exposure to ACE inhibitors for hypotension, oliguria, and hyperkalemia. If oliguria occurs, direct attention towards support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. Ramipril, 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.

To:

5.6 Fetal toxicity
Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue ALTACE as soon as possible [*see Use in Specific Populations (8.1)*].

6. Under **USE IN SPECIFIC POPULATIONS**, the section was changed from:

8.1 Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters) [*see WARNINGS AND PRECAUTIONS (5.6)*].

To:

8.1 Pregnancy

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue ALTACE as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue ALTACE unless it is considered life-saving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of *in utero* exposure to ALTACE for hypotension, oliguria, and hyperkalemia [*see Use in Specific Populations (8.4)*].

7. Under **USE IN SPECIFIC POPULATIONS/Pediatric Use**, the section was changed from:

8.4 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 ALTACE.

To:

Neonates with a history of in utero exposure to ALTACE:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. Ramipril, which crosses the placenta, can theoretically 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.

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 ALTACE.

8. Under **PATIENT COUNSELING INFORMATION**, the section was changed from:

17.4 Pregnancy

Inform female patients of childbearing age about the consequences of exposure to ACE inhibitors during pregnancy. Advise these patients to report pregnancies to their physicians as soon as possible.

To:

Female patients of childbearing age should be told about the consequences of exposure to Altace during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

9. The revision date and version number were updated.

There are no other changes from the last approved package insert.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any

labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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 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, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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 314.81(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.

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:

Lori Anne Wachter, RN, BSN
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

ENCLOSURE:
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
04/11/2012