DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 019901/S-064

SUPPLEMENT APPROVAL

Pfizer, Inc.
Attention: Marcio De Godoy
Senior Manager, Worldwide Safety and Regulatory
500 Arcola Road
Collegeville, PA 19423

Dear Mr. De Godoy:

Please refer to your Supplemental New Drug Application (sNDA) dated and received November 21, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Altace (ramipril) 1.25 mg, 2.50 mg, 5 mg, and 100 mg Capsules.

This supplemental new drug application provides for labeling revised as follows (additions are marked as underlined text and deletions are marked as ~~strikethrough text~~):

1. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS**, the following text was added/deleted:

   ~~ACE inhibitor use has been associated with the following:~~
   Angioedema, ~~with~~ increased risk in patients with a prior history ~~or when combined with mTOR inhibitors~~ (5.1)
   Hypotension and hyperkalemia (5.5, 5.8)
   Renal impairment: monitor renal function during therapy (5.3)
   ~~Increased risk of renal impairment when combined with another blocker of the renin-angiotensin-aldosterone system (5.7)~~
   Avoid concomitant use of an ACE inhibitor and angiotensin blocker ~~Avoid concomitant use with aliskiren in patients with moderate to severe renal impairment~~ (5.7)

2. Under **CONTRAINDICATIONS**, the following text was added/deleted:

   Do not co-administer ALTACE with aliskiren ~~with ALTACE~~:
   - in patients with diabetes.

3. Under **WARNINGS AND PRECAUTIONS**, the following text was added/deleted:

   5.7 Dual Blockade of the Renin-Angiotensin ~~Aldosterone~~ System
   Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on ALTACE and other agents that affect the RAS.

Aliskiren
Do not co-administer aliskiren with ALTACE in patients with diabetes. Avoid concomitant use of aliskiren with ALTACE in patients with renal impairment (GFR <60 mL/min/1.73 m^2). ~~*[see Drug Interactions (7.6)]*~~

4. Under **DRUG INTERACTIONS,** the following text was added/deleted:

7.2 Other Agents Affecting RAS

In general, avoid combined use of RAS inhibitors. *[see Warnings and Precautions (5.7)]*. Do not co-administer aliskiren with ALTACE in patients with diabetes *[see Contraindications (4)]*.

~~**7.2 Other Antihypertensive Agents**~~
~~Limited experience in controlled and uncontrolled trials combining ALTACE 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 drug classes lower blood pressure by inhibiting parts of the renin-angiotensin-aldosterone system.~~
~~The combination of ramipril and propranolol showed no adverse effects on dynamic parameters (blood pressure and heart rate).~~
~~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)]*.~~

~~**7.6 Aliskiren**~~

~~Do not co-administer aliskiren with ALTACE in patients with diabetes,~~ (b) (4) [redacted]

~~Avoid concomitant use of aliskiren with ALTACE in patients with renal impairment (GFR <60 mL/min/1.73 m^2) *[see Warnings and Precautions (5.7)]*.~~

~~**7.9 Other**~~

~~Neither ramipril nor its metabolites have been found to interact with food, digoxin, antacid, furosemide, cimetidine, indomethacin, and simvastatin. The co-administration of ramipril and warfarin did not adversely affect the anticoagulation effects of the latter drug. Additionally, co-administration of ramipril with phenprocoumon did not affect minimum phenprocoumon levels or interfere with the patients' state of anticoagulation.~~

5. The Table of Contents was updated to reflect the deleted text in Drug Interactions.

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(l)(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, PharmD.
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
05/02/2014