DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020125/S-016

SUPPLEMENT APPROVAL

Pfizer, Inc.
Attention: Sheetal Alur
Sr. Manager, Worldwide Safety and Regulatory
235 East 42nd Street
New York, NY 10017

Dear Ms. Alur:

Please refer to your Supplemental New Drug Application (sNDA) dated and received August 19, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Accuretic (quinapril/hydrochlorothiazide) 10/12.5 mg, 20/12.5 mg, and 20/25 mg Tablets.

We also refer to our January 17, 2014 approval letter which contained the following error: the label appended was an incorrect version: information about anaphylaxis with mTOR inhibitors was missing. This replacement approval letter incorporates the correction of the error. The effective approval date will remain January 17, 2014, the date of the original approval letter.

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. Under **PRECAUTIONS, General**, the following text was added/deleted:

> ~~**Derangements of**~~ **Serum Electrolyte Abnormalities:** In clinical trials, hyperkalemia (serum potassium ≥5.8 mmol/L) occurred in approximately 2% of patients receiving quinapril. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to 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.~~
>
> Hydrochlorothiazide can cause hypokalemia and hyponatremia. Hypomagnesemia can result in hypokalemia which appears difficult to treat despite potassium repletion. Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. The risk of hyperkalemia may be increased in patients with renal insufficiency, diabetes mellitus or with concomitant use of drugs that raise serum potassium (see Drug Interactions). The risk of hypokalemia may be increased in patients with cirrhosis, brisk diuresis, or with concomitant use of drugs that lower serum potassium. Monitor serum electrolytes periodically.

~~Treatment with thiazide diuretics has been associated with hypokalemia, hyponatremia, and hypochloremic alkalosis. These disturbances have sometimes been manifest as one or more of dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, nausea, and vomiting. Hypokalemia can also sensitize or exaggerate the response of the heart to the toxic effects of digitalis. The risk of hypokalemia is greatest in patients with cirrhosis of the liver, in patients experiencing a brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes, and in patients receiving concomitant therapy with corticosteroids or ACTH~~ (b) (4)

~~The opposite effects of quinapril and hydrochlorothiazide on serum potassium will approximately balance each other in many patients, so that no net effect upon serum potassium will be seen. In other patients, one or the other effect may be dominant. Initial and periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.~~

~~Chloride deficits secondary to thiazide therapy are generally mild and require specific treatment only under extraordinary circumstances (e.g., in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.~~

~~Calcium excretion is decreased by thiazides. In a few patients on prolonged thiazide therapy, pathological changes in the parathyroid gland have been observed, with hypercalcemia and hypophosphatemia. More serious complications of hyperparathyroidism (renal lithiasis, bone resorption, and peptic ulceration) have not been seen.~~

~~Thiazides increase the urinary excretion of magnesium, and hypomagnesemia may result.~~

Other Metabolic Disturbances:

Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients.

Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Monitor calcium levels in patients with hypercalcemia receiving Accuretic. ~~HCT. Thiazide diuretics raise serum levels~~

~~of cholesterol, triglycerides, and uric acid. These effects are usually minor, but frank gout or overt diabetes may be precipitated in susceptible patients.~~

[redacted] (b) (4)

Drug Interactions
Potassium Supplements and Potassium-Sparing Diuretics: ~~As noted above ("Derangements of Serum Electrolytes"), the net effect of ACCURETIC may be to elevate a patient's serum potassium, to reduce it, or to leave it unchanged.~~
Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. If concomitant use of such agents is indicated, ~~they should be given with caution, and the patient's serum potassium should be monitored~~ monitor serum potassium frequently.

[redacted] (b) (4)

Other Agents:

- ~~Quinapril treatment did not affect the pharmacokinetics of~~ Digoxin: Thiazide-induced electrolyte disturbances, i.e. hypokalemia, hypomagnesemia, increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events (See **PRECAUTIONS**).

2. Under **PRECAUTIONS, Drug Interactions,** a reference was added:

   Antidiabetic drugs (e.g., oral agents, insulin): Dosage adjustment of the antidiabetic drug may be required (see *Precautions*).

3. Under **ADVERSE REACTIONS**, **Postmarketing Experience**, the following text was added:

   EYE DISORDERS: acute myopia and acute angle closure glaucoma (see Warnings).

4. 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
01/17/2014