DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 012616/S-074 **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 Aldactazide (spironolctone/hydrochlorothiazide) 25/25 mg, and 50/50 mg Tablets.

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**, the following text was added/deleted:

Serum Electrolyte Abnormalities: Spironolactone 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). Hydrochlorothiazide can cause hypokalemia and hyponatremia. The risk of hypokalemia may be increased in patients with cirrhosis, brisk diuresis, or with concomitant use of drugs that lower serum potassium. Hypomagnesemia can result in hypokalemia which appears difficult to treat despite potassium repletion. Monitor serum electrolytes periodically.

~~All patients receiving diuretic therapy should be observed for evidence of fluid or electrolyte imbalance, e.g., hypomagnesemia, hyponatremia, hypochloremic alkalosis, and hypokalemia or hyperkalemia.~~

(b) (4)

~~Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and~~

~~can cause cardiac irregularities, which may be fatal. Consequently, no potassium supplement should ordinarily be given with ALDACTAZIDE.~~

~~If hyperkalemia is suspected (warning signs include paresthesia, muscle weakness, fatigue, flaccid paralysis of the extremities, bradycardia, and shock), an electrocardiogram (ECG) should be obtained. However, it is important to monitor serum potassium levels because mild hyperkalemia may not be associated with ECG changes.~~

~~If hyperkalemia is present, ALDACTAZIDE should be discontinued immediately. With severe hyperkalemia, the clinical situation dictates the procedures to be employed. These include the intravenous administration of calcium chloride solution, sodium bicarbonate solution, and/or the oral or parenteral administration of glucose with a rapid-acting insulin preparation. These are temporary measures to be repeated as required. Cationic exchange resins such as sodium polystyrene sulfonate may be orally or rectally administered. Persistent hyperkalemia may require dialysis.~~

~~Hypokalemia may develop as a result of profound diuresis, particularly when ALDACTAZIDE is used concomitantly with loop diuretics, glucocorticoids, or ACTH, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmias and may exaggerate the effects of digitalis therapy. Potassium depletion may induce signs of digitalis intoxication at previously tolerated dosage levels. Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.~~

~~ALDACTAZIDE therapy may cause a transient elevation of BUN. This appears to represent a concentration phenomenon rather than renal toxicity, since the BUN level returns to normal after use of ALDACTAZIDE is discontinued. Progressive elevation of BUN is suggestive of the presence of preexisting renal impairment.~~

~~Reversible hyperchloremic metabolic acidosis, usually in association with hyperkalemia, has been reported to occur in some patients with decompensated hepatic cirrhosis, even in the presence of normal renal function.~~

~~Dilutional hyponatremia, manifested by dryness of the mouth, thirst, lethargy, and drowsiness, and confirmed by a low serum sodium level, may be induced, especially when ALDACTAZIDE is administered in combination with other diuretics, and dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of sodium, except in rare instances when the hyponatremia is life-threatening. A true low-salt syndrome may rarely develop with ALDACTAZIDE therapy and may be manifested by increasing mental confusion similar to that observed with hepatic~~

~~coma. This syndrome is differentiated from dilutional hyponatremia in that it does not occur with obvious fluid retention. Its treatment requires that diuretic therapy be discontinued and sodium administered.~~

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 Aldactazide.

~~Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazides. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.~~

~~In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics.~~ (b) (4) ~~Thus, latent diabetes mellitus may become manifest during thiazide therapy.~~

~~The antihypertensive effects of ALDACTAZIDE may be enhanced in the post-sympathectectomy patient. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.~~

~~Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in patients on prolonged thiazide therapy.~~

Gynecomastia: Gynecomastia may develop in association with the use of spironolactone; physicians should be alert to its possible onset. The development of gynecomastia appears to be related to both dosage level and duration of therapy and is normally reversible when ALDACTAZIDE is discontinued. In rare

instances, some breast enlargement may persist when ALDACTAZIDE is discontinued.

Somnolence: Somnolence and dizziness have been reported to occur in some patients. Caution is advised when driving or operating machinery until the response to initial treatment has been determined.

Drug interactions:
ACE inhibitors Angiotensin II receptor antagonists, aldosterone blockers, potassium supplements, heparin, low molecular weight heparin, and other drugs known to cause hyperkalemia: Concomitant administration of ACE inhibitors with potassium-sparing diuretics has been associated with severe hyperkalemia.

Angiotensin II receptor antagonists, aldosterone blockers, heparin, low molecular weight heparin, and other drugs known to cause hyperkalemia: Concomitant administration may lead to severe hyperkalemia.

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

Digoxin: Spironolactone has been shown to increase the half-life of digoxin. This may result in increased serum digoxin levels and subsequent digitalis toxicity. ~~It may be necessary to reduce the maintenance and digitalization doses when spironolactone is administered, and the patient should be carefully monitored to avoid over- or underdigitalization.~~Monitor serum digoxin levels and adjust dose accordingly.

Thiazide-induced electrolyte disturbances, i.e. hypokalemia, hypomagnesemia, increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events (see *Precautions*).

(b) (4)

2. Under **ADVERSE REACTIONS**, Hydrochlorothiazide, the following text was added:

   Eye Disorders: acute myopia and acute angle closure glaucoma (*see Warnings*).

3. 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/

Lori A WACHTER
01/17/2014

MARY R SOUTHWORTH
01/17/2014