DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 012151/S-071

SUPPLEMENT APPROVAL

GD Searle LLC
Attention: Sheetal Alur
Senior Manager, Worldwide Regulatory Strategy
235 East 42nd Street
New York, NY 10017

Dear Ms. Alur:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 12, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aldactone (spironolactone) 25 mg, 50 mg, and 100 mg Tablets.

This "Prior Approval" 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 **CONTRAINDICATIONS**, the following text was added to the end of the section:

   ALDACTONE is contraindicated for patients with anuria, acute renal insufficiency, significant impairment of renal excretory function, hyperkalemia, Addison's disease or other conditions associated with hyperkalemia, and with concomitant use of eplerenone.

2. Under **WARNINGS,** the following text was added after the first paragraph in the section:

   Concomitant administration of ALDACTONE with the following drugs or potassium sources may lead to severe hyperkalemia:
   - other potassium-sparing diuretics
   - ACE inhibitors
   - angiotensin II antagonists
   - aldosterone blockers
   - non-steroidal anti-inflammatory drugs (NSAIDs), e.g., indomethacin
   - heparin and low molecular weight heparin
   - other drugs known to cause hyperkalemia
   - potassium supplements
   - diet rich in potassium
   - salt substitutes containing potassium

3. Under **PRECAUTIONS,** the following text was added/~~deleted~~ from the section:

   ~~Concomitant administration of potassium-sparing diuretics and ACE inhibitors or nonsteroidal anti-inflammatory drugs (NSAIDs), e.g., indomethacin, has been associated with severe hyperkalemia.~~

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.

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

Cholestyramine: Hyperkalemic metabolic acidosis has been reported in patients given ALDACTONE concurrently with cholestyramine.

4. Under **Adverse Reactions**, the following additions/~~deletions~~ were made:

~~Endocrine~~ Reproductive: Gynecomastia (see *Precautions*), inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, breast pain. Carcinoma of the breast has been reported in patients taking ALDACTONE but a cause and effect relationship has not been established.

Hematologic: Leukopenia (including agranulocytosis), thrombocytopenia.

Hypersensitivity: Fever, urticaria, maculopapular or erythematous cutaneous eruptions, anaphylactic reactions, vasculitis.

Metabolism: Hyperkalemia, electrolyte disturbances (see *Warnings* and *Precautions).*

Musculoskeletal: Leg cramps.

Nervous system /psychiatric: Lethargy, mental confusion, ataxia, dizziness, headache, drowsiness.

Liver / biliary: A very few cases of mixed cholestatic/hepatocellular toxicity, with one reported fatality, have been reported with ALDACTONE administration.

Renal: Renal dysfunction (including renal failure).

Skin: Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), alopecia, pruritis.

5. Under **DOSAGE AND ADMINISTRATION**, the heading "**Severe heart failure**" was changed to "**Severe heart failure in conjunction with standard therapy**".

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
06/12/2013