DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021437/S-011

SUPPLEMENT APPROVAL

GD Searle LLC
Attention: Lisa Malandro
Director, Worldwide Regulatory Strategy
235 East 42nd Street
New York, NY 10017

Dear Ms. Malandro:

Please refer to your Supplemental New Drug Application (sNDA) dated and received November 14, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Inspra (eplerenone) 25 mg and 50 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. In **HIGHLIGHTS/RECENT MAJOR CHANGES,** the following text was added:

Indications and Usage: Benefits of lowering blood pressure (1.3)	06/2012
Warnings and Precautions: Hyperkalemia (5.1)	05/2013
Drug Interactions: ACE Inhibitors and Angiotension II Receptor Antagonists (7.2)	05/2013

2. Under **WARNINGS AND PRECAUTIONS,** the following text was added:

5.1 Hyperkalemia

Minimize the risk of hyperkalemia with proper patient selection and monitoring, and avoidance of certain concomitant medications *[see CONTRAINDICATIONS (4), ADVERSE REACTIONS (6.2), and DRUG INTERACTIONS (7)]*.

Monitor patients for the development of hyperkalemia until the effect of INSPRA is established. Patients who develop hyperkalemia (>5.5 mEq/L) may continue INSPRA therapy with proper dose adjustment. Dose reduction decreases potassium levels *[see DOSAGE AND ADMINISTRATION (2.1)]*.

The rates of hyperkalemia increase with declining renal function *[see ADVERSE REACTIONS (6.2)]*.

Patients with hypertension who have serum creatinine levels >2.0 mg/dL (males) or >1.8 mg/dL (females) or creatinine clearance ≤50 mL/min should not be treated with INSPRA *[see CONTRAINDICATIONS (4)]*. Patients with CHF post-MI who have serum creatinine levels >2.0 mg/dL (males) or >1.8 mg/dL (females) or creatinine clearance ≤50mL/min should be treated with INSPRA with caution.

Diabetic patients with CHF post-MI should also be treated with caution, especially those with proteinuria. The subset of patients in the EPHESUS study with both diabetes and proteinuria on the baseline urinalysis had increased rates of hyperkalemia compared to patients with either diabetes or proteinuria *[see ADVERSE REACTIONS (6.2]*.

The risk of hyperkalemia may increase when eplerenone is used in combination with an angiotensin converting enzyme (ACE) inhibitor and/or an angiotensin receptor blocker (ARB) *[see DRUG INTERACTIONS (7.2)].*

3. Under **DRUG INTERACTIONS**, the following text was added:

7.2 ACE Inhibitors and Angiotensin II Receptor Antagonists

The risk of hyperkalemia may increase when eplerenone is used in combination with an angiotensin converting enzyme (ACE) inhibitor and/or an angiotensin receptor blocker (ARB). A close monitoring of serum potassium and renal function is recommended, especially in patients at risk for impaired renal function, e.g., the elderly. *[see WARNINGS AND PRECAUTIONS (5.1)]*

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
05/16/2013