DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021093/S-019

SUPPLEMENT APPROVAL

AstraZeneca Pharmaceuticals, LP
Attention: Ian Wogan
Regulatory Affairs Director
1 MedImmune Way
Gaithersburg, MD 20878

Dear Mr. Wogan:

Please refer to your Supplemental New Drug Application (sNDA) dated and received August 20, 2015, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Atacand HCT (candesartan cilexetil/hydrochlorothiazide) 16/12.5 mg, 32/12.5 mg, and 32/25 mg Tablets.

We also refer to your amendment dated January 29, 2016.

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, Metabolic Disturbances**, the following text was deleted from the third paragraph:

   Thiazides decrease urinary calcium excretion and may cause ~~mild~~ elevation of serum calcium. Avoid using ATACAND HCT in patients with hypercalcemia. (b) (4)

1. Under **PRECAUTIONS**, **Information for Patients** the following text was added:

   Hyperkalemia
   Tell patients receiving ATACAND HCT not to use potassium supplements, salt substitutes containing potassium, or other drugs that may increase serum potassium levels without consulting the prescribing physician.

2. Under **PRECAUTIONS**,**Drug Interactions** the following text was added:

   Interactions with Candesartan Cilexetil

   Dual Blockade of the Renin-Angiotensin System (RAS)

   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. Closely monitor blood pressure, renal function and electrolytes in patients on ATACAND HCT and other agents that affect the RAS.

   Do not co-administer aliskiren with ATACAND HCT in patients with diabetes. Avoid use of aliskiren with ATACAND HCT in patients with renal impairment (GFR <60 ml/min) (see CONTRAINDICATIONS).

Coadministration of ATACAND HCT with potassium sparing diuretics, potassium supplements, potassium-containing salt substitutes or other drugs that raise serum potassium levels may result hyperkalemia. Monitor serum potassium in such patients.

Interactions with Hydrochlorothiazide

Diazoxide − the hyperglycemic effect of diazoxide may be enhanced by thiazides.

Noradrenaline − Thiazides may decrease arterial responsiveness to noradrenaline, but not enough to preclude effectiveness of the pressor agent for therapeutic use.

Steroids or Adrenocorticotropic Hormone − Hypokalemia may develop during concomitant use of steroids or adrenocorticotropic hormone (ACTH).

Cytotoxic products − Thiazides may reduce the renal excretion of cytotoxic medicinal products (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

Cyclosporine − Concomitant treatment with cyclosporine may increase the risk of hyperuricemia and gout-type complications.

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, as amended, 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
02/09/2016