DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020838/S-039

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 (candesartan cilexetil) 4 mg, 8 mg, 16 mg, and 32 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. In **HIGHLIGHTS** the following information was revised:

RECENT MAJOR CHANGES

~~Indications and Usage, Hypertension (1.1) 02/2015~~
Warnings and Precautions (5.5, 5.6) 02/2016

DOSAGE AND ADMINISTRATION ----

	Starting Dose	**Target Dose ~~Range~~**	~~Target Maintenance Dose~~
Adult Hypertension (2.1)	16 mg tablet once daily	8 - 32 mg tablet total daily dose	
Pediatric Hypertension (1 to < 6 years) (2.2)	0.20 mg/kg oral suspension once daily	0.05 - 0.4 mg/kg oral suspension once daily or consider divided dose	
Pediatric Hypertension (6 to < 17 years) (2.2)	< 50 kg 4 – 8 mg tablet once daily > 50 kg 8 – 16 mg tablet once daily	< 50 kg 4 – 16 mg tablet once daily or consider divided dose > 50 kg 4 – 32 mg tablet once daily or consider divided dose	
Adult Heart Failure (2.3)	4 mg tablet once daily	32 mg tablet once daily[1]	(b) (4)

[1]The target dose is 32 mg once daily, which is achieved by doubling the dose at approximately 2-week intervals, as tolerated by patient

DRUG INTERACTIONS

- Lithium: Increases in serum lithium concentrations and toxicity (7).
- NSAIDS use may lead to increased risk of renal impairment and loss of antihypertensive effect (7).
- Combined~~Dual~~ inhibition of the renin-angiotension system: Increased risk of renal impairment, hypotension, and hyperkalemia (7).

2. Under **INDICATIONS AND USAGE**, the following cross-reference was added:

1.2 Heart Failure
ATACAND is indicated for the treatment of heart failure (NYHA class II-IV) in adults with left ventricular systolic dysfunction (ejection fraction ≤ 40%) to reduce cardiovascular death and to reduce heart failure hospitalizations *[see Clinical Studies (14.2)]*. ATACAND also has an added effect on these outcomes when used with an ACE inhibitor *[see Drug Interactions (7)]*.

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

5.5 Hyperkalemia
Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Concomitant use of ATACAND with drugs that may increase potassium levels may increase the risk of hyperkalemia *[see Drug Interactions (7)]*.
Monitor serum potassium periodically.

4. Under **DRUG INTERACTIONS**, the following text was added/deleted:

7.1 Agents Increasing Serum Potassium (b) (4)

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

7.2 Lithium
Increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists, including ATACAND. Monitor serum lithium levels.

~~Because candesartan is not significantly metabolized by the cytochrome P450 system and at therapeutic concentrations has no effects on P450 enzymes, interactions with drugs that inhibit or are metabolized by those enzymes would not be expected.~~

7.3 Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)
In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including candesartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving candesartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including candesartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

7.4 Combination ~~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. Triple combination of ATACAND with an ACE-inhibitor and a mineralocorticoid receptor antagonist is generally not recommended. Closely monitor blood pressure, renal function and electrolytes in patients on ATACAND and other agents that affect the RAS.
Do not co-administer aliskiren with ATACAND in patients with diabetes. Avoid use of aliskiren with ATACAND in patients with renal impairment (GFR <60 ml/min) *[see Contraindications (4)]*.

Triple combination of ATACAND with an ACE-inhibitor and a mineralocorticoid receptor antagonist is generally not recommended.

5. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics**, the following text was relocated from section 7:

   Because candesartan is not significantly metabolized by the cytochrome P450 system and at therapeutic concentrations has no effects on P450 enzymes, interactions with drugs that inhibit or are metabolized by those enzymes would not be expected.

6. Under **HOW SUPPLIED/STORAGE AND HANDLING**, the following text was deleted:

   NDC 0186-0016-31 unit of use bottles of 30
   NDC 0186-0016-54 unit of use bottles of 90
   ~~NDC 0186-0016-28 unit dose packages of 100.~~

   NDC 0186-0032-31 unit of use bottles of 30
   NDC 0186-0032-54 unit of use bottles of 90

   ~~NDC 0186-0032-28 unit dose packages of 100.~~

7. Under **PATIENT COUNSELING INFORMATION**, the following text was added/deleted:

   ~~See~~ Advise patient to read FDA-approved patient labeling (Patient Information).

   ~~17.1~~ Pregnancy
   ~~Female~~ Advise female patients of childbearing age should be told about the consequences of exposure to ATACAND during pregnancy. Discuss treatment options with women planning to become pregnant. Tell p~~P~~atients should be asked to report pregnancies to their physicians as soon as possible.

8. Multiple editorial revisions were made throughout the label (cross references were re-formatted, Orasweet trademark attribution was relocated to the end of the label)

9. 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