



NDA 020838/S-038

SUPPLEMENT APPROVAL

AstraZeneca
Attention: Ian Wogan
Director, Regulatory Affairs
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Dear Mr. Wogan:

Please refer to your Supplemental New Drug Application (sNDA) dated and received November 9, 2012, 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 acknowledge your amendments dated March 7, and April 4, 2013.

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:

Drug Interactions, Dual Blockade of the Renin-Angiotensin System (7) 04/2013

2. In **HIGHLIGHTS/CONTRAINDICATIONS**, the following was added/deleted:

Do not co-administer aliskiren with ATACAND in patients with diabetes (4).

3. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS**, the following text was deleted:

- ~~• Avoid fetal (in utero) and neonatal exposure (5.1).~~
- ~~• Children < 1 year of age must not receive ATACAND for hypertension (5.2).~~
- Observe for signs and symptoms of hypotension (5.3).
- ~~• Use with caution in patients with impaired hepatic (5.4) or renal (5.5) function.~~
- ~~• Monitor renal function (5.4) and potassium levels (5.5).~~
- ~~• Hyperkalemia may occur in heart failure patients treated with ATACAND (5.6).~~

4. In **HIGHLIGHTS/ADVERSE REACTIONS**, the following text was deleted:

~~Most common adverse reactions (incidence \geq 2% and greater than placebo) are back pain, dizziness, upper respiratory tract infection, pharyngitis and rhinitis (6.1).~~

5. In **HIGHLIGHTS/DRUG INTERACTIONS**, the following bullet was added:

- Dual inhibition of the renin-angiotensin system: Increased risk of renal impairment, hypotension, and hyperkalemia (7)

6. In **HIGHLIGHTS/USE IN SPECIFIC POPULATIONS**, the following bullet was deleted:

~~*Geriatrics:* No overall difference in efficacy or safety vs. younger adult patients, but greater sensitivity of some older individuals cannot be ruled out (8.5).~~

7. Under **DOSAGE AND ADMINISTRATION/Adult Hypertension**, the following text was added/deleted from the section:

~~No initial dosage adjustment is necessary for elderly patients, for patients with mildly impaired renal function, or for patients with mildly impaired hepatic function [see CLINICAL PHARMACOLOGY (12.3)]. In patients with moderate hepatic impairment, consideration should be given to initiation of ATACAND at a lower dose [see CLINICAL PHARMACOLOGY (12.3)]. For patients with possible depletion of intravascular volume (eg, patients treated with diuretics, particularly those with impaired renal function), ATACAND should be initiated under close medical supervision and consideration should be given to administration of a lower dose [see WARNINGS AND PRECAUTIONS (5.3)].~~

~~Use in Hepatic Impairment: Initiate with 8 mg ATACAND in patients with moderate hepatic insufficiency. Dosing recommendations cannot be provided for patients with severe hepatic insufficiency [see CLINICAL PHARMACOLOGY (12.3)].~~

8. Under **DOSAGE AND ADMINISTRATION/Pediatric Hypertension** 1 to < 17 years of age, the following cross reference was added/deleted from the tenth paragraph:

~~All pediatric patients with a glomerular filtration rate less than 30 ml/min/1.73m² should not receive ATACAND since ATACAND has not been studied in this population [see WARNINGS AND PRECAUTIONS (5.2) SPECIAL POPULATIONS (8)].~~

9. Under **CONTRAINDICATIONS**, the following text was added:

ATACAND is contraindicated in patients who are hypersensitive to candesartan. Do not administer aliskiren with ATACAND in patients with diabetes [see DRUG INTERACTIONS (7)].

10. Under **WARNINGS AND PRECAUTIONS/Hypotension**, the following text was added/deleted:

~~In adult or children patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (eg, those being treated with diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of ATACAND, or the treatment should start under close medical supervision [see DOSAGE AND ADMINISTRATION (2.1) and DRUG INTERACTIONS (7)].~~

~~If hypotension occurs, the patients should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment which usually can be continued without difficulty once the blood pressure has stabilized.~~

ATACAND can cause symptomatic hypotension. Symptomatic hypotension is most likely to occur in patients who have been volume and/or salt depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Patients with symptomatic hypotension may require temporarily reducing the dose of ATACAND, diuretic or both, and volume repletion. Volume and/or salt depletion should be corrected before initiating therapy with ATACAND.

~~Caution should be observed when initiating therapy in patients with heart failure. Patients with heart failure given ATACAND commonly have some reduction in blood pressure. In patients with symptomatic hypotension this may require temporarily reducing the dose of ATACAND, or diuretic, or both, and volume repletion. In the CHARM program (heart failure patients), hypotension was reported in 18.8% of patients on ATACAND versus 9.8% of patients on placebo. In the CHARM Added program, hypotension was reported in 22.6% of patients treated with ATACAND versus 13.8% treated with placebo. The incidence of hypotension leading to drug discontinuation in ATACAND-treated patients was 4.1% compared with 2.0% in placebo-treated patients. In the CHARM-Added program, where candesartan or placebo was given in addition to ACE inhibitors, hypotension was reported in 22.6% of patients treated with ATACAND versus 13.8% treated with placebo [see DRUG INTERACTIONS (7)].~~

Monitoring of blood pressure is recommended during dose escalation and periodically thereafter.

11. Under **WARNINGS AND PRECAUTIONS**, the section titled Impaired Hepatic Function was deleted.
12. Under **WARNINGS AND PRECAUTIONS/Impaired Renal Function**, the following text was added/deleted:

~~5.5 5.4 Renal Function Deterioration~~Impaired Renal Function

Monitor renal function periodically in patients treated with ATACAND. Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system. Patients whose renal function may depend, in part, on the activity of the renin-angiotensin system (e.g., patient with renal artery stenosis, chronic kidney disease, severe heart failure, or volume depletion) may be at particular risk of developing oliguria, progressive azotemia or acute renal failure when treated with ATACAND. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on ATACAND.

~~As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in some individuals treated with ATACAND. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (eg, patients with severe heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with ATACAND [see CLINICAL PHARMACOLOGY (12.3) and DRUG INTERACTIONS (7)].~~

~~In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There~~

~~has been no long term use of ATACAND in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.~~

~~In heart failure patients treated with ATACAND, increases in serum creatinine may occur. Dosage reduction or discontinuation of the diuretic or ATACAND, and volume repletion may be required. In the CHARM program (heart failure patients), the incidence of abnormal renal function (e.g., creatinine increase) was 12.5% in patients treated with ATACAND versus 6.3% in patients treated with placebo. In the CHARM-Added program, the incidence of abnormal renal function (eg, creatinine increase) was 15% in patients treated with ATACAND versus 9.0% in patients treated with placebo. The incidence of abnormal renal function (e.g., creatinine increase) leading to drug discontinuation in ATACAND-treated patients was 6.3% compared with 2.9% in placebo-treated patients. In the CHARM-Added program, where candesartan or placebo was given in addition to ACE inhibitors, the incidence of abnormal renal function (e.g., creatinine increase) was 15% in patients treated with ATACAND versus 9% in patients treated with placebo [see DRUG INTERACTIONS (7)].~~

~~Evaluation of patients with heart failure should always include assessment of renal function and volume status. Monitoring of serum creatinine is recommended during dose escalation and periodically thereafter.~~

~~Pediatrics—ATACAND has not been studied in children with estimated glomerular filtration rate < 30 mL/min/1.73m².~~

13. Under **WARNINGS AND PRECAUTIONS/Hyperkalemia**, the following text was added/deleted:

~~Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Monitor serum potassium periodically.~~

~~In heart failure patients treated with ATACAND, hyperkalemia may occur, especially when taken concomitantly with ACE inhibitors and potassium-sparing diuretics such as spironolactone [see DRUG INTERACTIONS (7)]. In the CHARM program (heart failure patients), the incidence of hyperkalemia was 6.3% in patients treated with ATACAND versus 2.1% in patients treated with placebo. In the CHARM-Added program, the incidence of hyperkalemia was 9.5% in patients treated with ATACAND versus 3.5% in patients treated with placebo. The incidence of hyperkalemia leading to drug discontinuation in ATACAND-treated patients was 2.4% compared with 0.6% in placebo-treated patients. In the CHARM-Added program where candesartan or placebo was given in addition to ACE inhibitors, the incidence of hyperkalemia was 9.5% in patients treated with ATACAND versus 3.5% in patients treated with placebo [see DRUG INTERACTIONS (7)]. During treatment with ATACAND in patients with heart failure, monitoring of serum potassium is recommended during dose escalation and periodically thereafter.~~

14. Under **ADVERSE REACTIONS/Clinical Studies Experience**, the following text was deleted:

~~Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.~~

Adult Hypertension

ATACAND has been evaluated for safety in more than 3600 patients/subjects, including more than 3200 patients treated for hypertension. About 600 of these patients were studied for at least 6 months and about 200 for at least 1 year. In general, treatment with ATACAND was well tolerated. The overall incidence of adverse events reported with ATACAND was similar to placebo.

The rate of withdrawals due to adverse events in all trials in patients (7510 total) was 3.3% (ie, 108 of 3260) of patients treated with ATACAND as monotherapy and 3.5% (ie, 39 of 1106) of patients treated with placebo. In placebo-controlled trials, discontinuation of therapy due to clinical adverse events occurred in 2.4% (ie, 57 of 2350) of patients treated with ATACAND and 3.4% (ie, 35 of 1027) of patients treated with placebo.

The most common reasons for discontinuation of therapy with ATACAND were headache (0.6%) and dizziness (0.3%).

The adverse events that occurred in placebo-controlled clinical trials in at least 1% of patients treated with ATACAND and at a higher incidence in candesartan cilexetil (n = 2350) than placebo (n = 1027) patients included back pain (3% vs. 2%), dizziness (4% vs. 3%), upper respiratory tract infection (6% vs. 4%), pharyngitis (2% vs. 1%), and rhinitis (2% vs. 1%).

~~The following adverse events occurred in placebo-controlled clinical trials at a more than 1% rate but at about the same or greater incidence in patients receiving placebo compared to ATACAND: fatigue, peripheral edema, chest pain, headache, bronchitis, coughing, sinusitis, nausea, abdominal pain, diarrhea, vomiting, arthralgia, albuminuria.~~

~~Other potentially important adverse events that have been reported, whether or not attributed to treatment, with an incidence of 0.5% or greater from the 3260 patients worldwide treated in clinical trials with ATACAND are listed below. It cannot be determined whether these events were causally related to ATACAND. **Body as a Whole:** asthenia, fever; **Central and Peripheral Nervous System:** paresthesia, vertigo; **Gastrointestinal System Disorder:** dyspepsia, gastroenteritis; **Heart Rate and Rhythm Disorders:** tachycardia, palpitation; **Metabolic and Nutritional Disorders:** creatine phosphokinase increased, hyperglycemia, hypertriglyceridemia, hyperuricemia; **Musculoskeletal System Disorders:** myalgia; **Platelet/Bleeding-Clotting Disorders:** epistaxis; **Psychiatric Disorders:** anxiety, depression, somnolence; **Respiratory System Disorders:** dyspnea; **Skin and Appendages Disorders:** rash, sweating increased; **Urinary System Disorders:** hematuria.~~

~~Other reported events seen less frequently included angina pectoris, myocardial infarction, and angioedema.~~

~~Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.~~

15. Under **ADVERSE REACTIONS/Postmarketing Experience**, the following text was added/deleted:

The following adverse reactions were identified during post-approval use of ATACAND. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following have been very rarely reported in post-marketing experience:

Digestive: Abnormal hepatic function and hepatitis.

Hematologic: Neutropenia, leukopenia, and agranulocytosis.

Immunologic: Angioedema

Metabolic and Nutritional Disorders: hyperkalemia, hyponatremia.

Renal: ~~renal impairment, renal failure~~

Respiratory system disorders: Cough

Skin and Appendages Disorders: Pruritus, rash and urticaria.

Rare reports of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

16. Under **ADVERSE REACTIONS**, the section titled **Laboratory Test Findings**, was deleted.

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

~~No significant drug interactions have been reported in studies of candesartan cilexetil given with other drugs such as glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide, and oral contraceptives in healthy volunteers, or given with enalapril to patients with heart failure (NYHA class II and III). 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.~~

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.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, and with some angiotensin II receptor antagonists. An increase in serum lithium concentration has been reported during concomitant administration of lithium with ATACAND., ~~so careful~~

~~monitoring of serum lithium levels is recommended during concomitant use. Monitor serum lithium levels.~~

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 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)].

18. Under **USE IN SPECIFIC POPULATIONS**, the section titled **Geriatric Use** was deleted.

19. Under the **Patient Information/Who should not take ATACAND?**, the following text was added:

Do not take ATACAND if you:

- are allergic to any of the ingredients in ATACAND. See the end of this leaflet for a complete list of ingredients in ATACAND.
- are diabetic and taking aliskiren.

20. Under the **Patient Information/ATACAND may cause serious side effects, including:**, the following text was deleted:

- ~~**Worsening liver problems.** Liver problems may get worse in people who already have liver problems, including inflammation of the liver and jaundice. Tell your doctor if you notice that your skin or the whites of your eyes turn yellow.~~

21. The revision date and version number was 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 Effectuated” (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
04/26/2013