DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021093/S-015

SUPPLEMENT APPROVAL

AstraZeneca Pharmaceuticals LP
Attention: Ian Wogan
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Wogan:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 14, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Atacand HCT (candesartan cilextetil/hydrochlorothiazide) 10/12.5 mg, 20/12.5 mg, and 20/25 mg Tablets.

We acknowledge receipt of your amendment dated March 8, 2012.

This "Prior Approval" supplemental new drug application provides for labeling revised as follows:

In Highlights:

1. The Boxed Warning was changed:

> **WARNING: FETAL TOXICITY**
> - **When pregnancy is detected, discontinue ATACAND HCT as soon as possible.**
> - **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. See Warnings: Fetal Toxicity.**

2. Under **WARNINGS,** the section was changed from:

   Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. Post-marketing experience has identified reports of fetal and neonatal toxicity in babies born to women treated with candesartan cilexetil during pregnancy. Because candesartan cilexetil is a component of ATACAND HCT, when pregnancy is detected, ATACAND HCT should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of ATACAND HCT as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, ATACAND HCT should be discontinued unless it is considered life saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Candesartan Cilexetil-Hydrochlorothiazide
There was no evidence of teratogenicity or other adverse effects on embryo-fetal development when pregnant mice, rats or rabbits were treated orally with candesartan cilexetil alone or in combination with hydrochlorothiazide. For mice, the maximum dose of candesartan cilexetil was 1000 mg/kg/day (about 150 times the maximum recommended daily human dose [MRHD]*). For rats, the maximum dose of candesartan cilexetil was 100 mg/kg/day (about 31 times the MRHD*). For rabbits, the maximum dose of candesartan cilexetil was 1 mg/kg/day (a maternally toxic dose that is about half the MRHD*). In each of these studies, hydrochlorothiazide was tested at the same dose level (10 mg/kg/day, about 4, 8, and 15 times the MRHD* in mouse, rats, and rabbit, respectively). There was no evidence of harm to the rat or mouse fetus or embryo in studies in which hydrochlorothiazide was administered alone to the pregnant rat or mouse at doses of up to 1000 and 3000 mg/kg/day, respectively.

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* Doses compared on the basis of body surface area. MRHD considered to be 32 mg for candesartan cilexetil and 12.5 mg for hydrochlorothiazide.

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

To:

Fetal Toxicity
Pregnancy category D
Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue ATACAND HCT as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue

ATACAND HCT, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to ATACAND HCT for hypotension, oliguria, and hyperkalemia (see PRECAUTIONS, Pediatric Use.)

Candesartan Cilexetil-Hydrochlorothiazide
There was no evidence of teratogenicity or other adverse effects on embryo-fetal development when pregnant mice, rats or rabbits were treated orally with candesartan cilexetil alone or in combination with hydrochlorothiazide. For mice, the maximum dose of candesartan cilexetil was 1000 mg/kg/day (about 150 times the maximum recommended daily human dose [MRHD]*). For rats, the maximum dose of candesartan cilexetil was 100 mg/kg/day (about 31 times the MRHD*). For rabbits, the maximum dose of candesartan cilexetil was 1 mg/kg/day (a maternally toxic dose that is about half the MRHD*). In each of these studies, hydrochlorothiazide was tested at the same dose level (10 mg/kg/day, about 4, 8, and 15 times the MRHD* in mouse, rats, and rabbit, respectively). There was no evidence of harm to the rat or mouse fetus or embryo in studies in which hydrochlorothiazide was administered alone to the pregnant rat or mouse at doses of up to 1000 and 3000 mg/kg/day, respectively.

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* Doses compared on the basis of body surface area. MRHD considered to be 32 mg for candesartan cilexetil and 12.5 mg for hydrochlorothiazide.

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

3. Under **PRECAUTIONS, Information for Patients** the section was changed from:

Pregnancy:
Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

To:

Pregnancy: Female patients of childbearing age should be told about the consequences of exposure to ATACAND HCT during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

4. Under **PRECAUTIONS, Pediatric Use**, a new section was added:

   Neonates with a history of in utero exposure to ATACAND HCT:

   If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

5. References to Pregnancy Category C and cross references to Fetal/Neonatal Morbidity and Mortality were deleted throughout the label.

6. 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, Pharm.D.
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
03/29/2012