DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200796/S-002

SUPPLEMENT APPROVAL

Takeda Pharmaceuticals North America
Attention: Ms. Beth-Anne Knapp, MBA, RAC
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Knapp:

Please refer to your Supplemental New Drug Application (sNDA) dated November 30, and received December 1, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Edarbi (azilsartan medoxomil) 40 and 80 mg Tablets.

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

1. In **HIGHLIGHTS** and **FULL PRESCRIBING INFORMATION**, the boxed warning was revised:

> **WARNING: FETAL TOXICITY**
> ***See full prescribing information for complete boxed warning.***
> - **When pregnancy is detected, discontinue Edarbi as soon as possible.** ***[see Warnings and Precautions (5.1)]***
> - **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.** ***[see Warnings and Precautions (5.1)]***

2. Under **WARNINGS AND PRECAUTIONS/Fetal/Neonatal Morbidity and Mortality**, the section was revised from:

5.1 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 during the second and third trimester. When pregnancy is detected, Edarbi 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 Edarbi 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 is available. In these rare cases, the mother should be apprised of the potential hazards to the fetus and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, Edarbi should be discontinued unless it is considered life-saving for the mother. Contraction stress testing, a nonstress test or biophysical profiling 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 a means of reversing hypotension and/or substituting for impaired renal function.

To:

5.1 Fetal toxicity

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 Edarbi as soon as possible. *[*see *Use in specific Populations (8.1]*

3. Under **USE IN SPECIFIC POPULATIONS/Pregnancy**, the section was revised from:

8.1 Pregnancy

Pregnancy Category C (first trimester) and D (second and third trimesters). There is no clinical experience with the use of Edarbi in pregnant women *[see Warnings and Precautions (5.1)]*.

To:

8.1 Pregnancy

Pregnancy Category D

Use of drugs that affect 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 Edarbi 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 Edarbi, 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 Edarbi for hypotension, oliguria, and hyperkalemia. [see *Use in Specific Populations(8.4)]*

4. Under **USE IN SPECIFIC POPULATIONS**, the following information was added to the section titled **Pediatric Use**:

8.4 Pediatric Use

Neonates with a history of in utero exposure to Edarbi:
If oliguria or hypotension occurs, support blood pressure and renal function.

5. Under **PATIENT COUNSELING INFORMATION**, the section was revised from:

17.1 General Information

Pregnancy: Female patients of childbearing age should be told that use of drugs like Edarbi that act on the renin-angiotensin system during pregnancy can cause serious problems in the fetus and infant including low blood pressure, poor development of skull bones, kidney failure, and death. These consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Discuss other treatment options with female patients planning to become pregnant. Women using Edarbi who become pregnant should notify their physicians as soon as possible *[see FDA-Approved Patient Labeling (17.2)]*.

To:

17.1 General Information

Pregnancy: Tell female patients of childbearing potential about the consequences of

exposure to Edarbi during pregnancy. Discuss treatment options with women planning to become pregnant. Tell patients to report pregnancies to their physicians as soon as possible.

6. The revision date and version number were updated.

The following changes were made to the Patient Package Insert:

1. Under **What is the most important information I should know about Edarbi?**, the section was revised from:

What is the most important information I should know about Edarbi?

Taking Edarbi during your second and third trimester can cause harm and even death to your unborn baby. If you think that you are pregnant, stop taking Edarbi and tell your doctor right away. If you plan to become pregnant, talk to your doctor about other ways to lower your blood pressure.

To:

What is the most important information I should know about Edarbi?

- Edarbi can cause harm or death to your unborn baby.
- Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant.
- If you become pregnant while taking Edarbi, tell your doctor right away. Your doctor may switch you to a different medicine to treat your high blood pressure.

2. 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, 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
12/14/2011