



NDA 200175/S-008

SUPPLEMENT APPROVAL

Daiichi Sankyo
Attention: Manini Patel
Director, Regulatory Affairs
399 Thornall Street
Edison, NJ 08837

Dear Ms. Patel:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 16, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tribenzor (olmesartan medoxomil/amlodipine/hydrochlorothiazide) 20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 and 40/10/25 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 changed:

<p style="text-align: center;">WARNING: FETAL TOXICITY</p> <ul style="list-style-type: none">• When pregnancy is detected, discontinue Tribenzor as soon as possible (5.1)• Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus (5.1)
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2. In **HIGHLIGHTS/RECENT MAJOR CHANGES**, the section was updated to include the changes to the Boxed Warning and Pregnancy sections.
3. Under **WARNINGS AND PRECAUTIONS**, the section was changed from:

5.1 Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system like olmesartan medoxomil can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature of patients who were taking angiotensin converting enzyme (ACE) inhibitors. When pregnancy is detected, discontinue Tribenzor 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 Tribenzor as soon as possible [*see Use in Specific Populations (8.1)*].

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, Tribenzor 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 **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 Tribenzor as soon as possible [*see Use in specific Populations (8.1)*].

4. Under **USE IN SPECIFIC POPULATIONS**, the section was changed from:

8.1 Pregnancy

Tribenzor. Pregnancy Categories C (first trimester) and D (second and third trimesters) [*see Warnings and Precautions (5.1)*].

Drugs that act directly on the renin-angiotensin system like olmesartan medoxomil can cause fetal and neonatal morbidity and death when administered to pregnant women. There have been several dozen cases reported in the world literature of patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, discontinue Tribenzor as soon as possible.

Healthcare professionals who prescribe drugs acting directly on the renin-angiotensin-aldosterone system should counsel women of childbearing potential about the risks of these agents during pregnancy [see *Nonclinical Toxicology* ([13.3](#))].

To:

8.1 Pregnancy

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 Tribenzor 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 Tribenzor, 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 Tribenzor for hypotension, oliguria, and hyperkalemia [see *Use in Specific Populations* (8.4)].

5. Under **USE IN SPECIFIC POPULATIONS/Pediatric Use**, a new section was added:

Neonates with a history of in utero exposure to Tribenzor:

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.

6. Under **PATIENT COUNSELING INFORMATION**, the section was changed from:

Physicians should instruct female patients of childbearing age about the consequences of second and third trimester exposure to drugs that act on the renin-angiotensin system and they should 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 informed to report pregnancies to their physicians as soon as possible. [See [Warnings and Precautions \(5.1\)](#) and [Use in Specific Populations \(8.1\)](#)].

To:

Pregnancy: Female patients of childbearing age should be told about the consequences of exposure to Tribenzor 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.

7. There are several editorial revisions noted throughout the label (i.e. the word “Tribenzor” is written in all caps in the **HIGHLIGHTS** section, the words “for oral use” were added to the **HIGHLIGHTS** section, and the words “provided as a tablet for oral administration” were added to the **DESCRIPTION** section)

The following changes were made to the Patient Package Insert (PPI):

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

If you become pregnant while taking Tribenzor, stop taking Tribenzor and call your doctor right away. Tribenzor can harm an unborn baby causing injury or even death. Talk to your doctor about other treatment options to lower your blood pressure before taking Tribenzor if you plan to become pregnant.

To:

- Tribenzor can cause harm or death to an unborn baby.
- Talk to your doctor about other ways to lower your blood pressure if you become pregnant.
- If you get pregnant while taking Tribenzor, tell your doctor right away.

2. Under **General Information about Tribenzor**, the website www.Tribenzor.com was added to the second paragraph.

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(1)(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
01/19/2012