



NDA 021286/S-021

SUPPLEMENT APPROVAL

Daiichi Sankyo, Inc.
Attention: Ms. Manini Patel
399 Thornall Street, 10th Floor
Edison, New Jersey 08837

Dear Ms. Patel:

Please refer to your Supplemental New Drug Application (sNDA) dated June 8, 2011, received June 9, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Benicar (olmesartan medoxomil) Tablets, 5, 20, and 40 mg.

This Prior Approval supplemental new drug application provides for revisions in accordance with the Guidance for Industry, *Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims*. In addition, language regarding pediatric use has been incorporated at the Division’s request. The following changes have been made (additions are shown as underlined text and deletions are shown as ~~strike through text~~):

In **HIGHLIGHTS OF PRESCRIBING INFORMATION**

1. Under **RECENT MAJOR CHANGES**, the following changes were made:

----- RECENT MAJOR CHANGES -----	
<u>Indications and Usage (1)</u>	<u>2/2012</u>
<u>Dosage and Administration</u>	
<u> Pediatric Hypertension (6 to 16 years of age) (2.2)</u>	<u>2/2012</u>
<u>Warnings and Precautions</u>	
<u> Morbidity in Infants (5.2)</u>	<u>2/2012</u>
Dosage and Administration, Use in pediatric hypertension (6 to 16 years of age) (2.2)	2/2010

2. Under **INDICATIONS AND USAGE**, the following changes were made:

- Benicar is an angiotensin II receptor blocker (ARB) indicated for the treatment of hypertension, alone or with other antihypertensive agents, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions (1).

Under **WARNINGS AND PRECAUTIONS**:

3. The following was added as the 2nd bullet:

- Children <1 year of age must not receive Benicar for hypertension (5.2).

In **FULL PRESCRIBING INFORMATION: CONTENTS***

4. The WARNING listing has been changed as follows:

WARNING—AVOID USE IN PREGNANCY

5. Under **5 WARNINGS AND PRECAUTIONS**, a new subsection listing “5.2 Morbidity in Infants” was added and the subsection numbers were updated for the “Hypotension in Volume- or Salt-Depleted Patients” listing from 5.2 to 5.3 and for the “Impaired Renal Function” listing from 5.3 to 5.4 as follows:

5.2 Morbidity in Infants

5.23 Hypotension in Volume- or Salt-Depleted Patients

5.34 Impaired Renal Function

In **FULL PRESCRIBING INFORMATION:**

6. Under **1 INDICATIONS AND USAGE**, the following was added:

Benicar is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including the class to which this drug principally belongs. There are no controlled trials demonstrating risk reduction with Benicar.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program’s Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

7. Under **2.2 Pediatric Hypertension (6 to 16 years of age)**, the following changes were made:

a) The following sentence was added after the first paragraph:

Children <1 year of age must not receive Benicar for hypertension.

b) At the end of the 2nd paragraph, the phrase “[see **Preparation of Suspension**]” has been deleted as follows:

Follow the suspension preparation instructions below to administer Benicar as a suspension ~~[see **Preparation of Suspension**].~~

8. Under **5. WARNINGS AND PRECAUTIONS**, the following changes were made:

a) The following new subsection has been added:

5.2 Morbidity in Infants

Children <1 year of age must not receive Benicar for hypertension. Drugs that act directly on the renin-angiotensin aldosterone system (RAAS) can have effects on the development of immature kidneys [see **Use in Specific Populations (8.4)**].

b) The subsection number for the “Hypotension in Volume- or Salt-Depleted Patients” header was updated from 5.2 to 5.3.

c) The subsection number for the “Impaired Renal Function” header was updated from 5.3 to 5.4.

9. Under **8.4 Pediatric Use**, the following was added after the first paragraph:

Benicar has not been shown to be effective for hypertension in children <6 years of age.

Children <1 year of age must not receive Benicar for hypertension [see **Warnings and Precautions (5.2)**]. The renin-angiotensin aldosterone system (RAAS) plays a critical role in kidney development. RAAS blockade has been shown to lead to abnormal kidney development in very young mice. Administering drugs that act directly on the renin- angiotensin aldosterone system (RAAS) can alter normal renal development.

10. Under **12.3 Pharmacokinetics, Pediatric**, the following was added after the first paragraph:

Olmесartan pharmacokinetics have not been investigated in pediatric patients less than 1 year of age [see **Warnings and Precautions (5.2)** and **Use in Specific Populations (8.4)**].

11. Under **14.1 Adult Hypertension**, the following was added as the last sentence of this subsection:

There are no trials of Benicar demonstrating reductions in cardiovascular risk in patients with hypertension, but at least one pharmacologically similar drug has demonstrated such benefits.

Minor editorial changes

12. Under **HIGHLIGHTS of PRESCRIBING INFORMATION**

- a) The trade name (“Benicar”) was changed to all uppercase letters (“BENICAR”) in the Highlights Limitation Statement and the Product Title Line.
- b) The dosage form and route of administration description in the Product Title Line was changed from “tablets” to “tablets, for oral use.”
- c) The revision date has been updated.

13. Throughout the labeling, the reference number in parentheses for “Hypotension in Volume- or Salt- Depleted Patients” that was previously 5.2 has been changed to 5.3.

14. Throughout the labeling, the reference number in parentheses for “Impaired Renal Function” that was previously 5.3 has been changed to 5.4.

We have completed our review of this supplemental application. 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).

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 contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
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/

NORMAN L STOCKBRIDGE
02/15/2012