

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
21-286**

Approval Letter



NDA 21-286

Sankyo Pharma, Inc.
Attention: Mr. Albert Yehaskel
780 Third Avenue, 47th Floor
New York, New York 10017

Dear Mr. Yehaskel:

Please refer to your new drug application (NDA) dated July 25, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Benicar (olmesartan medoxomil) Tablets, 5, 20, and 40 mg.

We acknowledge receipt of your submissions dated October 30, November 15, December 7, 20, and 31, 2001, and January 7, 23 and 30, February 13, March 1 and 7, and April 6 and 9, 2002. Your submission of April 6, 2002 constituted a complete response to our October 24, 2001 approvable letter.

This new drug application provides for the use of Benicar (olmesartan medoxomil) Tablets, 5, 20, and 40 mg for the treatment of hypertension.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling (package insert, immediate carton and container labels included in your submission of April 6, 2002). Accordingly, the application is approved effective on the date of this letter.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). Please note our letter of February 14, 2001 in which we denied your July 25, 2000 request for waiver of pediatric studies for hypertensive patients. We have agreed, however, to defer submission of your pediatric studies in hypertensive patients until March 6, 2005. In the interim, please submit your pediatric drug development plans within 120 days from the date of this letter and within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

In telephone conversations on April 23 and 24, 2002 between Dr. James Molt of Sankyo Pharma and Mr. Edward Fromm of the Division of Cardio-Renal Drug Products, it was agreed that the following changes to the package insert would be made at the time of the next printing:

1. Under **ADVERSE REACTIONS**, 3rd paragraph, the adverse events of “inflicted injury” and “upper respiratory tract infection” should be deleted.
2. Under **ADVERSE REACTIONS**, the listing of “other (potentially important) adverse events....in controlled or open-label trials” should be changed to:

Body as a Whole: chest pain, peripheral edema

Central and Peripheral Nervous System: vertigo

Gastrointestinal: abdominal pain, dyspepsia, gastroenteritis, nausea

Heart Rate and Rhythm Disorders: tachycardia

Metabolic and Nutritional Disorders: hypercholesterolemia, hyperlipemia, hyperuricemia

Musculoskeletal: arthralgia, arthritis, myalgia

Skin and Appendages: rash

3. Under **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility**, please delete from the second paragraph the words “for DNA damage in the rat kidney (comet assay).”
4. Under **OVERDOSAGE**, please delete the second paragraph, which makes reference to studies in mice, rats, and dogs.
5. Under **WARNINGS, Fetal/Neonatal Morbidity and Mortality**, the next to last sentence notes, among other things, drug associated “delays in developmental milestones.” This sentence should be modified to specify which *developmental milestones* were delayed.

Please submit these labeling changes in a supplemental application.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Robert Temple
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We acknowledge receipt of your submissions dated August 17, September 14 (two) and 28, October 5 and 25 (two), November 1 (two), 9, 14, 22, 27, and 29, December 8, 15, and 21, 2000, and January 4, 10, 26, and 31, February 5, 9, 15, 20, 22, 26, 27, and 28 (two), March 2, 7 (two), 12, 15, 16, 27 (two), 28 and 29, April 24, May 1, 7, 11, 15, 16 and 25, July 2 and 13, August 2, 14, 23 (two), 28, and 30, September 21 and 24, and October 5, 2001.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary to develop final printed labeling (FPL) for the drug. We have enclosed marked-up draft labeling, so that you can consider our recommended changes, but final labeling cannot be prepared until the issues described below can be addressed, and we may have further suggested changes. When you respond to these concerns you should submit modified proposed labeling.

It will be necessary for you to address fully our concerns related to the potential genotoxicity and carcinogenicity of olmesartan before approval can be granted. These concerns have focused on the interpretation of the *in vivo* mutation and clastogenicity assays and on the numerical excess of renal tumors seen in the two-year rat carcinogenicity study. These concerns may be addressed by one or both of the following:

- The collection and analysis of additional data.
- Further discussions and/or analyses of the currently available data.

Please remove the word Opadry from the immediate carton and container labels. It is not necessary to list inactive ingredients on the immediate container labels or on the carton labels. Therefore, you may choose one of the following two options:

1. Delete all reference to all inactive ingredients in the container labels and carton labels --or--
2. List the specific components of Opadry in the alphabetical list of inactive ingredients stated on the label but delete reference to Opadry per se.

Please supply a sample of the label that will be used on the container for shipping the bulk tablets for packaging from Germany to the United States. Blister and blister carton labels should also be submitted for review.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to

Food and Drug Administration
Rockville MD 20857

file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5313

Sincerely, 

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Marked-up Draft Labeling

12 pages redacted from this section of
the approval package consisted of draft labeling

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this page is the manifestation of the electronic signature.**

/s/

Robert Temple
10/24/01 02:42:47 PM

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the approval package consisted of draft labeling