CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20738/S001

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-738/S-001

OCT 28 1998

SmithKline Beecham Pharmaceuticals
Attention: Ms. Linda Rebar
1250 South Collegeville Road, UP4455
P.O. Box 5089
Collegeville, PA 19426-0989

Dear Ms. Rebar:

Please refer to your supplemental new drug application dated January 26, 1998, received January 26, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Teveten (eprosartan mesylate) 300 and 400 mg Tablets.

We acknowledge receipt of your submissions dated October 2, 1998.

Your submission of October 2, 1998 constituted a complete response to our September 23, 1998 action letter.

This supplemental new drug application provides for a new once daily dosing regimen and included final printed labeling revised as follows:

CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects: In the second paragraph, third sentence, "once- or" has been added. The sentence now begins, "Blood pressure control is maintained with once- or twice-daily dosing..."

CLINICAL PHARMACOLOGY, Clinical Trials: The second and third paragraphs have been revised to read as follows:

> The antihypertensive effects of *Teveten* were demonstrated principally in five placebo-controlled trials (4 to 13 weeks' duration) including dosages of 400 mg to 1200 mg given once daily (two studies), 25 mg to 400 mg twice daily (two studies), and one study directly comparing total daily doses of 400 mg to 800 mg given once daily or twice daily. The five studies included 1111 patients randomized to eprosartan and 395 patients randomized to placebo. The studies showed dose-related antihypertensive responses.
>
> At study endpoint, patients treated with *Teveten* at doses of 600 mg to 1200 mg given once daily experienced significant decreases in sitting systolic and diastolic blood pressure at trough, with differences from placebo of approximately 5-10/3-6 mmHg. Limited experience is available with the dose of 1200 mg administered once daily. In a direct comparison of 200 mg to 400 mg b.i.d. with 400 mg to 800 mg o.d. of *Teveten*, effects at trough were similar. Patients treated with *Teveten* at doses of 200 mg to 400 mg given twice daily experienced significant decreases in sitting systolic and diastolic blood pressure at trough, with differences from placebo of approximately 7-10/4-6 mmHg.

The fourth paragraph has been revised to read as follows:

> Peak (1 to 3 hours) effects were uniformly, but moderately, larger than trough effects with b.i.d. dosing, with the trough-to-peak ratio for diastolic blood pressure 65% to 80%. In the once-daily dose-response studies, trough-to-peak response of • 50% were observed at some doses (including 1200 mg), suggesting attenuation of effect at the end of the dosing interval.

PRECAUTIONS, Geriatric Use: The third sentence has been revised to read, "In a study of only patients over the age of 65, *Teveten* at 200 mg twice daily (and increased optionally up to 300 mg twice daily) decreased diastolic blood pressure on average by 3 mmHg (placebo corrected).

ADVERSE REACTIONS, Laboratory Test Findings: A new sentence has been added at the end of this subsection: "Patients were rarely withdrawn from Teveten because of laboratory test results."

ADVERSE REACTIONS, Creatinine, Blood Urea Nitrogen: The second sentence has been revised to read, "Two patients were withdrawn from clinical trials for elevations in serum creatinine and BUN, and three additional patients were withdrawn for increases in serum creatinine."

ADVERSE REACTIONS, Hemoglobin: In the second sentence, "Eight" has been replaced by "Two" in the sentence, " Two patients were withdrawn from clinical trials for anemia."

ADVERSE REACTIONS, Neutropenia: The second sentence has been revised to read, "No patient was withdrawn from any clinical trials for neutropenia."

ADVERSE REACTIONS, Thrombocytopenia: In the second sentence, "Three" has been replaced by "Four" in the sentence "Four patients receiving Teveten in clinical trials were withdrawn for thrombocytopenia."

ADVERSE REACTIONS, Serum Potassium: In the second sentence, "Two patients were" has been replaced with "One patient was" and "five" has been replaced with "three" in the sentence, "One patient was withdrawn from clinical trials for hyperkalemia and three for hypokalemia."

DOSAGE AND ADMINISTRATION: The first paragraph has been replaced with the following:

> "The usual recommended starting dose of Tevetan is 600 mg once daily when used as monotherapy in patients who are not volume depleted (See WARNINGS, Hypotension in Volume-and/or Salt-Depleted Patients). Tevetan can be administered once or twice daily with total daily doses ranging from 400 mg to 800 mg. There is limited experience with doses beyond 800 mg/day.
>
> If the anti-hypertensive effect measured at trough using once-daily dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response. Achievement of maximum blood pressure reduction in most patients may take 2 to 3 weeks."

In what is now the third paragraph, in the second sentence, "of" has been replaced with "with," to read, "Discontinuation of treatment with eprosartan..."

HOW SUPPLIED: "Rx only" has been added.

We have completed the review of this supplemental application 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 included in your October 2, 1998 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

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, contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
(301) 594-5334

Sincerely yours,

/S/ 10/28/98

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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SEP 23 1998

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Dear Ms. Rebar:

Please refer to your supplemental new drug application dated January 26, 1998, received January 26, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Teveten (eprosartan mesylate) 300 and 400 mg Tablets.

We acknowledge receipt of your submissions dated May 15 and 26, August 21 and September 14, 1998. The user fee goal date for this application is January 26, 1999.

This supplement application provides for draft labeling revised under **DOSAGE AND ADMINISTRATION, CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects** and **Clinical Trials, PRECAUTIONS, Geriatric Use**, and **ADVERSE REACTIONS, Laboratory Test Findings**.

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 for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed marked-up draft.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material.

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

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 this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
(301) 594-5334

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
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Enclosure