CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-012

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-012

SB Pharmco Puerto Rico Inc. d/b/a GlaxoSmithKline
Attention: Ms. Catherine K. Clark
One Franklin Plaza
200 N. 16th Street, FP1005
Philadelphia, PA 19102

Dear Ms. Clark:

Please refer to your new drug application (NDA) dated December 21, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coreg CR (carvedilol phosphate) Extended-Release 10, 20, 40, and 80 mg Capsules.

We acknowledge receipt of your submissions dated February 7, 2006, March 24 and 31, April 21, June 30, July 10, September 15 (two), 18, 22 (two), 26 (two), and October 5 (two), 6 (two), and 18, 2006.

This new drug application provides for the use of Coreg CR (carvedilol phosphate) Extended-Release Capsules for mild-to-severe heart failure, to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction $\leq$ 40%, and essential hypertension.

The Division of Scientific Investigations inspection found problems at sites in your study 369. We were particularly concerned about the [redacted] site, problems at which appeared to be of a nature that should have been detected in your monitoring and auditing process. After careful review, we concluded that essential results of the study were not impacted by these problems, so we were able to rely upon the results of 369 to support extension of claims to the heart failure population. However, we strongly recommend that you review the monitoring and auditing process and its results for study 369. We would be interested in seeing the results of such a review.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted labeling (immediate container and carton labels submitted October 18, 2006). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

We recommend the following dissolution methods and specifications. The dissolution method is USP [(b) (4)]. The vessel volume is [(b) (4)]. The [(b) (4)] specification expressed as % label claim is not more than [(b) (4)], not less than [(b) (4)] and not more than [(b) (4)] not less than [(b) (4)] and not more than [(b) (4)], and not less than [(b) (4)]

We remind you of your agreement to address the use of [(b) (4)] microparticles in full-scale drug product manufacture by conducting additional stability studies a----eed at the September 20, 2006 teleconference and specified in your submission dated September 26, 2006. Please include side-by-side dissolution profiles for the [(b) (4)] microparticles and the final drug products manufactured using these microparticles, as discussed during the above referenced teleconference. These stability studies will be performed in addition to the standard stability studies carried on the first three commercial batches of each strength, and the data will be reported in the annual report.

We also remind you of your agreement to tighten the acceptance criteria for particle size distribution in the drug substance, residual solvents in the drug substance and microparticles, and drug product dissolution, as warranted by the analysis of data obtained on the [(b) (4)] commercial drug product batches, as agreed at the September 20, 2006 teleconference and specified in your submission dated September 26, 2006. The progress of the studies and final tightening of the acceptance criteria, along with the analysis of the results, will be reported via the annual report.

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. We are waiving the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert(s) directly 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

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 Melissa Robb, Regulatory Health Project Manager, at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.

Director
Division of Cardio-Renal Products
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/

Norman Stockbridge
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