**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-012/S-004

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

Dear Ms. Clark:

Please refer to your supplemental new drug application (NDA) dated April 19, 2007, 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 also refer to your amendment dated September 12, 2007.

This supplemental new drug application provides for the following modifications to the package insert and patient package insert of Coreg CR:

1) To modify the established name in the header of the package insert (PI) and patient package insert (PPI)

From:

"(carvedilol phosphate) Extended-Release Capsules"

To:

"(carvedilol phosphate) Extended-release Capsules"

2) To add a cross-reference "(…see **PRECAUTIONS, Drug Interactions**)" to the end of the sentence under **CLINICAL PHARMACOLOGY, Pharmacokinetic Drug-Drug Interactions, Digoxin**.

3) To add the sentence "The results of COMET are presented in Table 1 below." to the **CLINCAL TRIALS, The COMET Trial** section of the PI to be consistent with the latest PI approved for Coreg IR (February 23, 2007).

4) To add the sentence "The effect on mortality was primarily due to a reduction in cardiovascular death." to the **CLINCAL TRIALS, The COMET Trial** section of the PI to be consistent with the latest PI approved for Coreg IR (February 23, 2007).

5) To add "Table 1. Results of COMET" and the approved wording and table representing the COMET secondary endpoints to the **CLINCAL TRIALS, The COMET Trial** section of the PI to be consistent with the latest PI approved for Coreg IR (February 23, 2007).

6) To change case sensitivity of the trade name for metoprolol succinate in the **CLINCAL TRIALS, The COMET Trial** section of the PI

From:

"Toprol XL"

To:

"TOPROL-XL"

7) To modify the dependent variable in the **CLINICAL TRIALS, Trials in Severe Heart Failure** section of the PI, "Figure 1. Survival Analysis for COPERNICUS (intent-to-treat)" to be consistent with the latest PI approved for Coreg IR

From:

"% Survival"

To:

"% Mortality"

8) To modify the dependent variable in the **CLINICAL TRIALS, Left Ventricular Dysfunction Following Myocardial Infarction** section of the PI, "Figure 3. Survival Analysis for CAPRICORN (intent-to-treat)" to be consistent with the latest PI approved for Coreg IR

From:

"% Survival"

To:

"% Mortality"

9) To add "(…and PRECAUTIONS, Drug Interactions)" as a reference to the end of the sentence under **INDICATIONS AND USAGE, Heart Failure** due to the potential concomitant use with digitalis.

10) To add the statements "Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia." to the **PRECAUTIONS, Drug Interactions** section of the PI.

11) To modify the subsection name in the **PRECAUTIONS, Drug Interactions** section of the labeling

From:

"Digoxin"

To:

"Digitalis Glycosides"

12) To delete the sentence "Both digoxin and carvedilol slow AV conduction." from the **PRECAUTIONS, Drug Interactions** section of the labeling.

13) To add the cross-reference "(…see **CLINICAL PHARMACOLOGY, Pharmacokinetic Drug-Drug Interactions**)" to the **PRECAUTIONS, Drug Interactions** section of the labeling.

14) To modify the **PRECAUTIONS, Pediatric Use** section of the PI to be consistent with the latest PI approved for Coreg IR with the exception of two differences in which the Coreg IR approved labeling uses the brand name "COREG" in place of the established name "carvedilol" and "immediate-release carvedilol", respectively (see underlined text)

From:

"Safety and efficacy of carvedilol in patients younger than 18 years of age have not been established."

To:

"Effectiveness of carvedilol in patients younger than 18 years of age has not been established.

In a double-blind trial, 161 children (mean age 6 years, range 2 months to 17 years; 45% less than 2 years old) with chronic heart failure [NYHA class II-IV, left ventricular ejection fraction <40% for children with a systemic left ventricle (LV), and moderate-severe ventricular dysfunction qualitatively by echo for those with a systemic ventricle that was not an LV] who were receiving standard background treatment were randomized to placebo or to 2 dose levels of carvedilol. These dose levels produced placebo-corrected heart rate reduction of 4-6 heart beats per minute, indicative of beta-blockade activity. Exposure appeared to be lower in pediatric subjects than adults. After 8 months of follow-up, there was no significant effect of treatment on clinical outcomes. Adverse reactions in this trial that occurred in greater than 10% of patients treated with immediate-release carvedilol and at twice the rate of placebo-treated patients included chest pain (17% versus 6%), dizziness (13% versus 2%), and dyspnea (11% versus 0%)."

15) To add the following statement to the **DOSAGE AND ADMINISTRATION, Left Ventricular Dysfunction Following Myocardial Infarction** section of the PI after the third sentence: "A lower starting dose may be used (10 mg once daily) and/or, the rate of up-titration may be slowed if clinically indicated (e.g., due to low blood pressure or heart rate, or fluid retention)." to be consistent with the latest PI approved for Coreg IR.

16) To add the statement "TOPROL-XL is a registered trademark of the AstraZeneca group of companies." to the **STORAGE** section of the PI.

17) Other very minor grammatical updates have been added to the PI (e.g., hyphens).

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon electronic labeling text. We will transmit the SPL version of the labeling submitted on September 12, 2007 to the National Library of Medicine for public dissemination.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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 Dan Brum, Pharm.D., MBA, Regulatory Health Project Manager, at (301)796-0578.

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

cc: Enclosed Labeling Text

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

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/s/

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Norman Stockbridge

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