DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-012/S-010
NDA 22-012/S-013

GlaxoSmithKline
Attention: Catherine K. Clark
Director, US Regulatory Affairs
One Franklin Plaza
200 N. 16th Street, MS 1005
Philadelphia, PA 19102

Dear Ms. Clark:

Please refer to your supplemental new drug applications dated April 23, 2008 (S-010) and December 16, 2008 (S-013), submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Coreg CR (carvedilol phosphate) 10 mg, 20 mg, 40 mg, and 80 mg Extended Release Capsules.

We acknowledge receipt of your submissions dated December 22, 2008 and March 10, 2009 (S-010), as well as your e-mail dated June 23, 2009.

These "Changes Being Effected" supplemental new drug applications provide for changes to the **HIGHLIGHTS**, **DOSAGE AND ADMINISTRATION**, **WARNINGS AND PRECAUTIONS**, and **USE IN SPECIFIC POPULATIONS** sections of the label as well as changes to the **PATIENT INFORMATION LEAFLET**. The following revisions were proposed:

1. In **HIGHLIGHTS/RECENT MAJOR CHANGES**, the following has been added:

   Warnings and Precautions, Hypotension (5.3) December 2008

2. In **DOSAGE AND ADMINISTRATION**, the sentence "Subsequent titration to higher or lower doses may be necessary as clinically warranted" has been removed as the last sentence from the first paragraph.

3. In **DOSAGE AND ADMINISTRATION**, the following has been added to Table 1:

   When switching from carvedilol 12.5 mg or 25 mg twice daily, a starting dose of COREG CR 20 mg or 40 mg once daily, respectively, may be warranted for elderly patients or those at increased risk of hypotension, dizziness, or syncope. Subsequent titration to higher doses should, as appropriate, be made after an interval of at least two weeks.

4. In **DOSAGE AND ADMINISTRATION**, the following has been added:

   2.5 Geriatric Use
   When switching elderly patients (65 years of age or older) who are taking the higher doses of immediate-release carvedilol tablets (12.5 mg or 25 mg twice daily) to COREG CR, a lower starting dose of COREG CR should be considered to minimize the potential for dizziness, syncope, or hypotension *[see Dosage and Administration (2)]*.Patients who have switched and who tolerate COREG CR should, as appropriate, have their dose increased after an interval of at least two weeks *[see Use in Specific Populations (8.5)]*

5. In **WARNINGS AND PRECUATIONS/Hypotension**, the first paragraph has been modified from:

In clinical trials of primarily mild-to-moderate heart failure with immediate-release carvedilol, hypotension and postural hypotension occurred in 9.7% and syncope in 3.4% of patients receiving carvedilol compared to 3.6% and 2.5% of placebo patients, respectively. The risk for these events was highest during the first 30 days of dosing, corresponding to the up-titration period and was a cause for discontinuation of therapy in 0.7% of carvedilol patients, compared to 0.4% of placebo patients. In a long-term, placebo-controlled trial in severe heart failure (COPERNICUS), hypotension and postural hypotension occurred in 15.1% and syncope in 2.9% of heart failure patients receiving carvedilol compared to 8.7% and 2.3% of placebo patients, respectively. These events were a cause for discontinuation of therapy in 1.1% of carvedilol patients, compared to 0.8% of placebo patients.

To:

In clinical trials of primarily mild-to-moderate heart failure with immediate-release carvedilol, hypotension and postural hypotension occurred in 9.7% and syncope in 3.4% of patients receiving carvedilol compared to 3.6% and 2.5% of placebo patients, respectively. The risk for these events was highest during the first 30 days of dosing, corresponding to the up-titration period and was a cause for discontinuation of therapy in 0.7% of carvedilol patients, compared to 0.4% of placebo patients. In a long-term, placebo-controlled trial in severe heart failure (COPERNICUS), hypotension and postural hypotension occurred in 15.1% and syncope in 2.9% of heart failure patients receiving carvedilol compared to 8.7% and 2.3% of placebo patients, respectively. These events were a cause for discontinuation of therapy in 1.1% of carvedilol patients, compared to 0.8% of placebo patients.

In a trial comparing heart failure patients switched to COREG CR or maintained on immediate-release carvedilol, there was a 2-fold increase in the combined incidence of hypotension, syncope or dizziness in elderly patients (> 65 years) switched from the highest dose of carvedilol (25 mg twice daily) to COREG CR 80 mg once daily *[see Use In Specific Populations (8.5), DOSAGE AND ADMINISTRATION (2)]*

6. In **USE IN SPECIFIC POPULATIONS/Geriatric Use**, the word “initial” has been added to the first sentence of the first paragraph.

7. In **USE IN SPECIFIC POPULATIONS/Geriatric Use**, the following has been added as the second paragraph:

   A randomized study (n = 405) comparing mild to severe heart failure patients switched to COREG CR or maintained on immediate-release carvedilol included 220 patients who were 65 years of age or older. In this elderly subgroup, the combined incidence of dizziness, hypotension, or syncope was 24% (18/75) in patients switched from the highest dose of immediate-release carvedilol (25 mg twice daily) to the highest dose of COREG CR (80 mg once daily) compared to 11% (4/36) in patients maintained on immediate-release carvedilol (25 mg twice daily). When switching from the higher doses of immediate-release carvedilol to COREG CR, a lower starting dose is recommended for elderly patients *[see Dosage and Administration (2.5)]*

8. In the **PATIENT INFORMATION LEAFLET/What are possible side effects of COREG CR**?, the following has been added as the ninth bullet:

- **rare but serious allergic reactions** (including hives or swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing) have happened in patients who were on

COREG or COREG CR. These reactions can be life-threatening. In some cases, these reactions happened in patients who had been on COREG before taking COREG CR.

We have completed our review of these applications, as amended, and they are approved, effective on the date of this letter, for use as recommended in the agreed upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] is structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert), upon receipt, we will transmit that version of the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 22-012/S010, NDA 22-012/S013.**"

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
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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:

Lori Anne Wachter, RN, BSN
Regulatory Project Manager
(301) 796 3975

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: agreed upon labeling text

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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