DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020297/S-034, S-035

SUPPLEMENT APPROVAL

SmithKline Beecham
Attention: Linda Rebar
Director, Global Regulatory Affairs
2301 Renaissance Blvd.
PO Box 61540, RN0420
King of Prussia, PA 19406-2772

Dear Ms. Rebar:

Please refer to your Supplemental New Drug Applications (sNDAs) dated December 16, 2009 (S-034) and November 22, 2010 (S-035), received December 16, 2009 and November 22, 2010, respectively, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Coreg (carvedilol) 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg Tablets.

Your September 1, 2010, submission constituted a complete response to our June 10, 2010, action letter for S-034.

S-034 proposes patient friendly text regarding hypertension to the Patient Information Leaflet as follows:

1. In the **PATIENT INFORMATION LEAFLET,** under **What is COREG?** the bullets were reordered to appear as they do in the package insert and now appear as follows:

   • to treat patients with certain types of heart failure
   • to treat patients who had a heart attack that worsened how well the heart pumps
   • to treat patients with high blood pressure (hypertension)

2. In the **PATIENT INFORMATION LEAFLET,** the following information was added to the end of the leaflet:

   What is high blood pressure (hypertension)?
   Blood pressure is the force of blood in your blood vessels when your heart beats and when your heart rests. You have high blood pressure when the force is too much. High blood pressure makes the heart work harder to pump blood through the body and causes damage to blood vessels. COREG can help your blood vessels relax so your blood pressure is lower. Medicines that

lower blood pressure may lower your chance of having a stroke or heart attack.

3. The revision date and version number were updated.

We also refer to our letter dated September 23, 2010, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Beta-blockers. This information pertains to the risk of withdrawing beta-blockers prior to major surgery. The following changes were made for **S-035**:

1. In **HIGHLIGHTS/RECENT MAJOR CHANGES**, the section was revised to include the changes for Major Surgery as follows:

Warnings and Precautions, Major Surgery (5.9)	October 2010

2. Under **FULL PRESCRIBING INFORMATION/WARNINGS AND PRECAUTIONS**, the section titled **5.9 Anesthesia and Major Surgery** was revised, and now reads:

5.9 Major Surgery

3. Under **FULL PRESCRIBING INFORMATION/DRUG INTERACTIONS,** the heading **7.9 Anesthesia** was added.

4. Under **WARNINGS AND PRECAUTIONS/Major Surgery**, the text was revised from:

5.9 Anesthesia and Major Surgery
If treatment with COREG CR is to be continued perioperatively, particular care should be taken when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used *[see Overdosage (10) for information on treatment of bradycardia and hypertension]*.

To:

5.9 Major Surgery
Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

5. Under **DRUG INTERACTIONS**, the text regarding anesthesia was relocated and now reads as follows:

7.9 Anesthesia
If treatment with COREG CR is to be continued perioperatively, particular care should be taken when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used *[see Overdosage (10) for information on treatment of bradycardia and hypertension]*.

6. The revision date and version number were updated.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements and any annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

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}

Mary Ross Southworth, Pharm.D.
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

MARY R SOUTHWORTH
01/06/2011