DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-297/S-030

GlaxoSmithKline
Attention: Ms. Catherine Clark
One Franklin Plaza
200 N. 16th Street
Philadelphia, PA 19102

SUPPLEMENT APPROVAL

Dear Ms. Clark:

Please refer to your supplemental new drug application (NDA) dated June 11, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coreg (carvedilol) 3.125, 6.25, 12.5, and 25 mg Tablets.

This supplemental new drug application provides for the following revisions to the package insert:

1. Add the following text to **HIGHLIGHTS OF PRESCRIBING INFORMATION**, **DRUG INTERACTIONS**:

   Amiodarone may increase carvedilol levels resulting in further slowing of the heart rate or cardiac conduction. (7.6).

2. Add the following text to the **DRUG INTERACTIONS** section of the PI:

   Amiodarone, and its metabolite desethyl amiodarone, inhibitors of CYP2C9 and P-glycoprotein, increased concentrations of the S(-) enantiomer of carvedilol by at least 2-fold *[see Clinical Pharmacology (12.5)]*. The concomitant administration of amiodarone or other CYP2C9 inhibitors such as fluconazole with Coreg may enhance the β-blocking properties of carvedilol resulting in further slowing of the heart rate or cardiac conduction. Patients should be observed for signs of bradycardia or heart block, particularly when one agent is added to pre-existing treatment with the other.

3. Add the following text to the **CLINICAL PHARMACOLOGY/Drug-Drug Interactions** section of the PI:

   Amiodarone: In a pharmacokinetic study conducted in 106 Japanese patients with heart failure, co-administration of small loading and maintenance doses of amiodarone with carvedilol resulted in a two-fold increase in the steady-state trough concentrations of S-carvedilol *[see Drug Interactions (7.6)]*.

4. The **CLINICAL PHARMACOLOGY/Drug-Drug Interactions** has been reordered alphabetically and a cross-reference was added to Digoxin and Rifampin, specifically "*[see Drug Interactions (7.5)]*".

5. In accordance with 201.57(a)(5) and subsequent to the 1-year period, the sponsor removed Recent Major Changes for "Warnings and Precautions, Glycemic control in Type 2 Diabetes (5.6)".

6. "Drug Interactions December 2008" is added to the Recent Major Changes section of the **HIGHLIGHTS OF PRESCRIBING INFORMATION.**

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

Within 21 days of the date of this letter, 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, we will transmit that version 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., Regulatory 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—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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