DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-297/S-011

GlaxoSmithKline
Attention: Ms. 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 dated August 18, 2003 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.

We acknowledge receipt of your submissions dated August 26, 2003 (two).

This supplemental new drug application provides for revised labeling that consolidates the safety section and removes the warning regarding hepatic injury. The revisions to the draft labeling are as follows:

1. In the **CLINICAL PHARMACOLOGY/Special Populations/Hepatic Impairment** subsection, the following was deleted at the end of the first sentence, "(see WARNINGS, Hepatic Injury)".

2. In the **WARNINGS** section, the **Hepatic Injury** subsection has been deleted.

3. In the **PRECAUTIONS/Geriatric Use** subsection, the first sentence of the first paragraph was changed from:

   Of the 765 patients with congestive heart failure randomized to COREG in US clinical trials, 31% (235) were 65 years of age or older.

   To:

   Of the 765 patients with congestive heart failure randomized to COREG in US clinical trials, 31% (235) were 65 years of age or older, and 7.3% (56) were 75 years of ago or older.

4. In the **PRECAUTIONS/Geriatric Use** subsection, the second sentence of the first paragraph was changed from:

   Of the 1,156 patients randomized to COREG in a long-term, placebo-controlled trial in severe heart failure, 47% (547) were 65 years of age or older.

   To:

   Of the 1,156 patients randomized to COREG in a long-term, placebo-controlled trial in severe heart failure, 47% (547) were 65 years of age or older, and 15% (174) were 75 years of age or older.

5. In the **PRECAUTIONS/Geriatric Use** subsection, the following sentence was deleted as the last sentence of the first two paragraphs:

   There were no notable differences in efficacy or the incidence of adverse events between older and younger subjects.

6. In the **PRECAUTIONS/Geriatric Use** subsection, the end of the subsection was changed from:

   There were no notable differences in efficacy or the incidence of adverse events between older and younger subjects. With the exception of dizziness (incidence 8.8% in the elderly vs. 6% in younger patients), there were no events for which the incidence in the elderly exceeded that in the younger population by greater than 2.0%.

   Similar results were observed in a postmarketing surveillance study of 3,328 COREG patients, of whom approximately 20% were 65 years of age or older.

   To:

   With the exception of dizziness in hypertensive patients (incidence 8.8% in the elderly vs 6% in younger patients), no overall differences in the safety or effectiveness (See Figures 2 and 4) were observed between the older subjects and younger subjects in each of these populations. Similarly, other reported clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

7. In the beginning of the **ADVERSE REACTIONS** section, the following was added:

   COREG has been evaluated for safety in patients with congestive heart failure (mild, moderate, and severe heart failure), in patients with left ventricular dysfunction following myocardial infarction and in hypertensive patients. The observed adverse event profile was consistent with the pharmacology of the drug and the health status of the patients in the clinical trials. Adverse events reported for each of these patient populations are provided below. Excluded are adverse events considered too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population. Rates of adverse events were generally similar across demographic subsets (men and women, elderly and non-elderly, blacks and non-blacks).

8. In the **ADVERSE REACTIONS/Congestive Heart Failure** subsection, the following was deleted as the third sentence of the first paragraph of the subsection:

   The adverse experience profile of COREG in patients with congestive heart failure was consistent with the pharmacology of the drug and the health status of the patients.

9. In **Table 2. Adverse Events (% Occurrence) Occurring More Frequently with COREG Than With Placebo in Patients With Mild-to-Moderate Heart Failure Enrolled in US Heart Failure Trials or in Patients With Severe Heart Failure in the COPERNICUS Trial (Incidence >3% in Patients Treated with Carvedilol, Regardless of Causality**), the following adverse events were deleted:

   Pain
   Sinusitis
   Bronchitis
   Upper Respiratory Infection

10. In the **ADVERSE REACTIONS/Congestive Heart Failure** subsection, the third paragraph was changed from:

    In addition to the events in Table 2, in these trials chest pain, injury, cardiac failure, abdominal pain, gout, insomnia, depression, anemia, viral infection, and dyspnea were also reported, but rates were equal or greater in placebo treated patients. Rates of adverse events were generally similar across demographic subsets (men and women, elderly and non-elderly, blacks and non-blacks).

    To:

    Cardiac failure and dyspnea were also reported in these studies, but the rates were equal or greater in patients who received placebo.

11. In the **ADVERSE REACTIONS/Congestive Heart Failure/Incidence >1% to ≤3%/Body as a Whole** subsection, the following adverse events were deleted:

    Infection, back pain

12. In the **ADVERSE REACTIONS/Congestive Heart Failure/Incidence >1% to ≤3%** subsection, the following subsection was deleted:

    Resistance Mechanism: Infection

13. In the **ADVERSE REACTIONS/Congestive Heart Failure** subsection, the following was deleted from the end of the subsection:

    Postmarketing Experience: The following adverse reaction has been reported in postmarketing experience: reports of aplastic anemia have been rare and received only when carvedilol was administered concomitantly with other medications associated with the event.

14. In the **ADVERSE REACTIONS/Left Ventricular Dysfunction Following Myocardial Infarction** subsection, the following was deleted at the end of the first sentence of the second paragraph, "as well as the health status of the patient".

15. In the **ADVERSE REACTIONS/Left Ventricular Dysfunction Following Myocardial Infarction** subsection, the third sentence of the second paragraph of the subsection was deleted, "Hypertension and myocardial infarction were also reported, but rates were equal or greater in placebo treated patients".

16. In the **ADVERSE REACTIONS/Left Ventricular Dysfunction Following Myocardial Infarction** subsection, the following was deleted at the end of the fourth sentence of the second paragraph of the subsection, "urinary tract infection".

17. In **Table 3. Adverse Events in US Placebo-Controlled Hypertension Trials Incidence ≥1%, Regardless of Causality**, the following adverse events were deleted:

    Resistance Mechanism
        Viral Infection
    Respiratory
        Pharyngitis
    Urinary/Renal
        Urinary Tract Infection

18. In the **ADVERSE REACTIONS/Hypertension** subsection, the third paragraph was changed from:

    In addition to the events in Table 3, abdominal pain, back pain, chest pain, dependent edema, dyspepsia, dyspnea, fatigue, headache, injury, nausea, pain, rhinitis, sinusitis, somnolence, and upper respiratory tract infection were also reported, but rates were equal or greater in placebo treated patients. Rates of adverse events were generally similar across demographic subsets (men and women, elderly and non-elderly, blacks and non-blacks).

    To:

    Dyspnea and fatigue were also reported in these studies, but the rates were equal or greater in patients who received placebo.

19. In the **ADVERSE REACTIONS/Hypertension/ Incidence .0.1% to ≤1%/Gastrointestinal** subsection, the reference at the end of was changed from:

    see WARNINGS, Hepatic Injury

    To:

    see Laboratory Abnormalities

20. In the **ADVERSE REACTIONS/Hypertension** subsection, the last two paragraphs of the subsection have been changed from:

    Other adverse events occurred sporadically in single patients and cannot be distinguished from concurrent disease states or medications.

    COREG therapy has not been associated with clinically significant changes in routine laboratory tests in hypertensive patients. No clinically relevant changes were noted in serum potassium, fasting serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

    To:

    Laboratory Abnormalities:
    Reversible elevations in serum transaminases (ALT or AST) have been observed during treatment with COREG. Rates of transaminase elevations (2- to 3-times the upper limit of normal) observed during controlled clinical trials have generally been similar between patients treated with COREG and those treated with placebo. However, transaminase elevations, confirmed by rechallenge, have been observed with COREG. In a long-term, placebo-controlled trial in severe heart failure, patients treated with COREG had lower values for hepatic transaminases than patients treated with placebo, possibly because COREG-induced improvements in cardiac function led to less hepatic congestion and/or improved hepatic blood flow.

    COREG therapy has not been associated with clinically significant changes in serum potassium, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine. No clinically relevant changes were noted in fasting serum glucose in hypertensive patients; fasting serum glucose was not evaluated in the congestive heart failure clinical trials.

    Postmarketing Experience:

The following adverse reaction has been reported in postmarketing experience: reports of aplastic anemia have been rare and received only when carvedilol was administered concomitantly with other medications associated with the event.

We have completed our review of this application, as amended. This application 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 submitted labeling (package insert submitted August 18, 2003).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-297/S-011" Approval of this submission by FDA is not required before the labeling is used.

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, HFD-410
FDA
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:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Doug Throckmorton

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