CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-297/S-009

Chemistry Review(s)
<table>
<thead>
<tr>
<th>CHEMIST'S REVIEW</th>
<th>1. ORGANIZATION</th>
<th>2. NDA Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HFD - 110</td>
<td>20-297</td>
</tr>
</tbody>
</table>

3. Name and Address of Applicant (City & State)

GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

4. Supplement #

SE1-009
Date Sep. 27, 2002

5. Drug Name

Coreg

6. Nonproprietary Name

Carvedilol

7. Supplement Provides For:

FFICACY SUPPLEMENT
the CAPRICORN trial to evaluate the safety and efficacy of carvedilol in patients with a recent myocardial infarction (< 21 days) and left ventricular dysfunction.

8. Amendments & other (reports, etc) - Dates

SE1-009 (SC)
Date Nov. 25, 2002

9. Pharmacological Category

Hypertension

10. How Dispensed

/ / RX / / OTC

11. Related IND(s)/NDA(s)/DMF(s)

12. Dosage Form(s)

Tablets

13. Potencies

3.125 mg, 6.25 mg, 12.5 mg, and 25 mg

14. Chemical Name and Structure

\((\pm)\text{-1-(Carbazol-4-yloxy}-3-\text{[2-(o-methoxyphenoxy)ethyl]amino)}-2\text{-propanol}

15. Records/Reports Current

/ / Yes / / No
Reviewed

/ / Yes / / No

16. Comments:

The amendment of Nov. 25, 2002 provided Environmental Assessment statement for Categorical Exclusion.

17. Conclusions and Recommendations:

The applicant requested a waiver of the requirement for an environmental assessment. As provided under 21 CFR 25.31(b), the applicant stated that this action will not cause the concentration of the drug substance at the point of entry into the aquatic environment to be 1 ppb or greater. The applicant does not have knowledge of any extraordinary circumstances that might cause this action to have a significant affect on the quality of the human environment.

Categorical exclusion is acceptable under 21 CFR 25.31 (b) and from CMC point of view this supplement may be approved.

18. REVIEWER

Ramsharan D. Mittal
ENVIRONMENTAL ASSESSMENT

Statement of Categorical Exclusion

For

Coreg®
(carvedilol, SK&F-105517)

DATE: 25 November 2002

APPLICANT: SmithKline Beecham Corporation d/b/a GlaxoSmithKline

ADDRESS: One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

STATEMENT: The proposed action is subject to the categorical exclusion listed in 21 CFR Part 25.31(b). GlaxoSmithKline has reviewed market forecasts, indications, and dosage information, and estimates that this action will not cause the concentration of the drug substance active moiety to be one part per billion (1 ppb) or greater at the point of entry into the aquatic environment. GlaxoSmithKline does not have knowledge of any extraordinary circumstances that might cause this action to have a significant affect on the quality of the human environment.
CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-297/S-009

Statistical Review(s)
STATISTICAL REVIEW AND EVALUATION
(ampendement of Clinical/Statistical Review of 12/04/02)

NDA #: 20-297
SERIAL #: SE8-009
DRUG NAME: Coreg (carvedilol)
INDICATION: to reduce mortality and the risk of infarction in clinically stable patients who have survived the acute phase of a myocardial infarction
SPONSOR: Glaxo SmithKline

DOCUMENT REVIEWED:
1. SAS data base in EDR

STATISTICAL REVIEWER: H.M. James Hung, Ph.D. (HFD-710)
MEDICAL REVIEWER: Norman Stockbridge, M.D. (HFD-110)

STATISTICAL KEY WORDS: Change of primary endpoint, alpha allocation

Distribution: NDA 20-297, SE8-009
  HFD-110/Dr. Throckmorton
  HFD-110/Dr. Stockbridge
  HFD-700/Dr. Anello
  HFD-710/Dr. Chi
  HFD-710/Dr. Mahjoob
  HFD-710/Dr. Hung
  HFD-710/chron

JHung/301-594-5436/DB1/capricorn1.doc/12-9-2002
The following table is to replace Table 10 of the clinical/statistical review dated 12/4/02, as a result of some minor changes because a few patients (six in the placebo group and one in the carvedilol group) were hospitalized and died on the same dates. These minor changes did not affect the reviewers’ conclusions in the 12/4/02 review.

Table 10a. Time to event for death or cardiovascular hospitalization

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>CV hosp only</th>
<th>Death only</th>
<th>Death after hosp</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=216</td>
<td>Carvedilol N=224</td>
<td>Placebo N=78</td>
</tr>
<tr>
<td>Rand to hosp</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>163</td>
<td>145</td>
<td>____</td>
</tr>
<tr>
<td>Median</td>
<td>98</td>
<td>81</td>
<td>____</td>
</tr>
<tr>
<td>Rand to death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>____</td>
<td>____</td>
<td>187</td>
</tr>
<tr>
<td>Median</td>
<td>____</td>
<td>____</td>
<td>148</td>
</tr>
<tr>
<td>Hosp to death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>____</td>
<td>____</td>
<td>____</td>
</tr>
<tr>
<td>Median</td>
<td>____</td>
<td>____</td>
<td>____</td>
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</tbody>
</table>