CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-297/S-009

Chemistry Review(s)

CHEMIST'S REVIEW	1. ORGANIZATION HFD - 110	2. NDA Number 20-297
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	8. Amendments & other(reports, etc) - Dates
7. Supplement Provides For: FFICACY SUPPLEMENT the CAPRICORN trial to evaluate the safety and efficacy of carvedilol in patients with a recent myocardial infraction (< 21 days) and left ventricular dysfunction.		SE1-009 (BC) Date Nov. 25, 2002
9. Pharmacological Category Hypertension	10. How Dispensed /X/ 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 (±)-1-(Carbazol-4-yloxyl)-3-{[2-(o-methoxyphenoxy) ethyl]amino}-2-propanol		15.Records/Reports Current /__/ Yes /__/ No Reviewed /x/ 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

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

/s/

Ramsharan Mittal
3/26/03 03:28:24 PM
CHEMIST

J. V. Advani
3/26/03 04:06:22 PM
CHEMIST

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)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION
(amendment 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

Time (days)	CV hosp only		Death only		Death after hosp	
	Placebo N=216	Carvedilol N=224	Placebo N=78	Carvedilol N=65	Placebo N=73	Carvedilol N=51
Rand to hosp			—	—		
Mean	163	145			133	95
Median	98	81			68	51
Rand to death	—	—				
Mean			187	195	276	223
Median			148	93	233	185
Hosp to death	—	—	—	—		
Mean					142	128
Median					66	48