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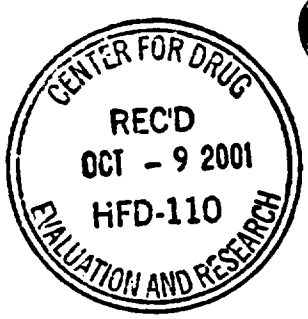
APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-297/S-007

Correspondence

Desk Copy: Zelda McDonald



GlaxoSmithKline

October 3, 2001

NDA 20-297 (S-007)
COREG® (carvedilol) Tablets

GlaxoSmithKline
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P.O. Box 5089
Collegeville, PA
19426-0989

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Robert Temple, M.D., Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research (HFD-40)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Response to FDA Comments/FDA Meeting (September 19, 2001) and Facsimile (September 27, 2001)

Dear Dr.Temple:

Reference is made to NDA 20-297 Supplement (S-007) for *Coreg* (carvedilol) tablets that was submitted to FDA on March 2, 2001. Reference is also made to the approvable action letter for Supplement 007 and the related meeting with FDA on September 19, 2001 to discuss the content of final printed labeling. In preparation for approving submission of final printed labeling, the Agency requested the following:

- Reasons for differences in results of analyses for primary and secondary endpoints obtained by GSK and FDA. (The response is provided in Attachment 1). On September 28, 2001, GSK and Dr. Norman Stockbridge discussed the response in a telecon. Dr. Stockbridge indicated that he understood the response submitted by GSK and had no further questions.

- Additional written support for inclusion of the following statement in the Clinical Trials/COPERNICUS section of Prescribing Information: "Patients' global assessments showed significant improvement following treatment with carvedilol in COPERNICUS". (The response is provided in Attachment 2.)

- Revisions to Adverse Events Tables: Round off values for adverse events to the nearest whole number; capture events that have equal frequency among Coreg treated patients and placebo treated patients in text under the respective table. (The labeling is revised as requested and is contained in Appendix B; please refer to Adverse Events Tables 2, 3 and 4.)

We also make reference to your FAX of September 26, 2001 in which the following additional requests were made:

- Clinical Trials Section: Indicate by statement if COPERNICUS results relative to hospitalizations were different or similar in demographic subgroups (i.e., elderly, males versus females and blacks versus whites).

GSK included the following statement in the Clinical Trials section of Prescribing Information: "Coreg had a consistent and beneficial effect on all-cause mortality as well as the combined endpoints of all-cause mortality plus hospitalization (total, CV or for heart failure) in the overall study population and in all subgroups examined, including men and women, elderly and non-elderly, black and non-black." (Please refer to Volume 4, pp. 000017 to 000020 and 000116 of NDA 20-297 (S-007) dated February 28, 2001.)

- Adverse Events in COPERNICUS: Indicate by statement if adverse events were different or similar across demographic subgroups.

GSK included the following statement in the section on Adverse Reactions/COPERNICUS: "Rates of adverse events were generally similar across demographic subsets (men and women, elderly and non-elderly, blacks and non-blacks)." (Please refer to Attachment 3.)

- Adverse Events in Hypertensive Patients: Indicate by statement if adverse events were different or similar in demographic subgroups.

GSK included the following statement in the section on Adverse Events/Hypertension: "The overall incidence of adverse experiences was similar when hypertensive patients were compared by age, sex, or racial origins in studies conducted both by SmithKline Beecham and Boehringer." (Please refer to the Integrated Summary of Safety in volume 1.91, page 000108, paragraph 3 of approved NDA 20-297 submitted on March 31, 1993.)

Following discussions with the Division on October 2, 2001 to clarify comments in the aforementioned Facsimile, GSK was able to complete all labeling revisions requested by FDA. Accordingly, enclosed are: 1) an index to the changes made to draft labeling as provided in our submission dated September 14, 2001 (Appendix A); 2) an edited version of the new draft labeling in which *underline* denotes addition to text and *strikethrough* denotes deletion to text (Appendix B); and, 3) an unedited (clean) version of the new draft labeling (Appendix C). GSK greatly appreciates the several opportunities we have had to interact with the Agency in order that we reach agreement on content of final printed labeling.

If you have questions regarding this submission, please contact me by telephone at 610-917-5368.

Sincerely,

Catherine K. Clark
Director
North America Regulatory Affairs

Desk Copy: Drs. Hung, Lipicky, Stockbridge, and Temple

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confidential

commercial

information

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ORIGINAL

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NDA 20-297 (S-007)
Coreg® (carvedilol) Tablets

June 4, 2001

NDA 20-297 (S-007)
COREG® (carvedilol) Tablets

NDA SUPP AMEND
SE1-007
(BM)

Raymond J. Lipicky, M.D., Director
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products (HFD-110)
Attn: Document Control Room 5002
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Lipicky:
Reference is made to NDA 20-297 (S-007) for COREG® (carvedilol) Tablets, which was submitted to FDA on March 2, 2001. The Supplement contained a single clinical study report, Protocol 287, entitled, "A Multicenter randomized double-blind, placebo-controlled study to determine the effect of carvedilol on mortality in patients with severe chronic heart failure (MF 4477/SB 287)". The study enrolled 2,289 patients from 334 centers and 21 countries. The listing of investigators who participated in Study 287 is contained in the Supplement.

In accordance with an agreement with the Division, we committed to provide financial disclosure information for Supplement S-007 before or on June 4, 2001. Accordingly and consistent with 21 CFR 54.4 (a) (1), enclosed is signed Form FDA 3454 and a related attachment. The attachment contains the names of 6 clinical investigators who did not respond to repeated requests for financial disclosure. However, regarding all investigators participating in Study 287, there was 1) no financial arrangement with any investigator whereby the value of the compensation to the investigator could be affected by the outcome of the study and 2) no investigator was the recipient of significant payments as defined in 21 CFR 54.2(f).

Please do not hesitate to contact me by telephone at (610) 917-5368 or by facsimile at (610) 917-4708 should you have any questions regarding this submission.

Sincerely,

Catherine K. Clark

Catherine K. Clark
Director
NA Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-297

SmithKline Beecham Pharmaceuticals
Attention: Ms. Catherine K. Clark
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Dear Ms. Clark:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Coreg (carvedilol) Tablets
Review Priority Classification:	Priority (P)
NDA Number:	20-297
Supplement number:	S-007
Date of supplement:	February 28, 2001
Date of receipt:	March 2, 2001

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 1, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 2, 2001.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852

If you have any question, please call:

Ms. Zelda McDonald
Regulatory Project Manager
(301) 594-5333

Sincerely,

/S/ 4/27/01

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation, I
Center for Drug Evaluation and Research