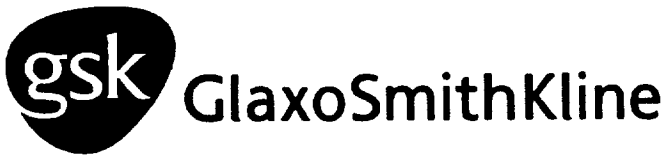
CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-297/S-007

Administrative Documents



NDA 20-297 (S-007)

Coreg® (carvedilol) Tablets

Item 13/14 Patent Information

ORIGINAL

GlaxoSmithKline

28 February 2001

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

Tel. 215 751 4000
Fax. 215 751 3400
www.gsk.com

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration, Park Bldg., Rm. 2-14
12420 Parklawn Dr.
Rockville, MD 20857

NDA SUPP AMEND
SE1-007
(X R)

Re: sNDA No. 20-297 (S-007)
Time Sensitive Patent Information

Dear Sirs:

In accordance with 21 C.F.R. 314.53, the following patent information is being submitted.

Patent No.	Expiration Date	Type of Patent	Patent Owner	Representative of Patent Owner
4,503,067	March 5, 2007	Drug	Boehringer Mannheim GmbH	Mary E. McCarthy Corporate Intellectual Property GlaxoSmithKline Corporation 709 Swedeland Road Mail Code UW2220 King of Prussia, PA 19406

Patent No.	Expiration Date	Type of Patent	Patent Owner	Representative of Patent Owner
5,760,069	June 7, 2015	Method of Use (Decreasing Mortality caused by Congestive Heart Failure)	Boehringer Mannheim Pharmaceuticals Corporation-SmithKline Beecham Corporation Limited Parnership #1	Mary E. McCarthy Corporate Intellectual Property GlaxoSmithKline Corporation 709 Swedeland Road Mail Code UW2220 King of Prussia, PA 19406

The undersigned declares that U.S. Patent Number 5,760,069 covers the method of use of COREG (Carvedilol) for decreasing mortality caused by congestive heart failure. This product is currently approved under Section 505 of the Federal Food, Drug and Cosmetic Act.

Patent No.	Expiration Date	Type of Patent	Patent Owner	Representative of Patent Owner
5,902,821	February 7, 2016	Method of Use (Treating Congestive Heart Failure)	Boehringer Mannheim Pharmaceuticals Corporation-SmithKline Beckman Corporation Limited Parnership No. 1	Mary E. McCarthy Corporate Intellectual Property GlaxoSmithKline Corporation 709 Swedeland Road Mail Code UW2220 King of Prussia, PA 19406

The undersigned declares that U.S. Patent Number 5,902,821 covers the method of use of COREG (Carvedilol) for treating congestive heart failure. This product is currently approved under Section 505 of the Federal Food, Drug and Cosmetic Act.

Please advise the undersigned if further information is required.

This letter is being submitted in duplicate.

Very truly yours,

Catherine K. Clark

Catherine K. Clark
Title, Director
N.A. Regulatory Affairs

n:\mem\carvedil\fda5.doc

Item 13/14 - Patent Information

The following patent information is being submitted pursuant to 21 C.F.R. 314.53.

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By: Catherine K. Clark

Title: Director

Date: February 28, 2001

Patent No.	Expiration Date	Type of Patent	Patent Owner	Representative of Patent Owner
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The undersigned declares that U.S. Patent Number 5,902,821 covers the method of use of COREG (Carvedilol) for treating congestive heart failure. This product is currently approved under Section 505 of the Federal Food, Drug and Cosmetic Act.

By: Catherine L Clark

Title: Director

Date: February 28, 2001

EXCLUSIVITY SUMMARY FOR NDA # __20-297_____ SUPPL #__007____

Trade Name __Coreg_____ Generic Name __carvedilol_____

Applicant Name __GlaxoSmithKline_____ HFD # ___110_____

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /___/ NO /_X__/

b) Is it an effectiveness supplement?

YES /_X__/ NO /___/

If yes, what type? (SE1, SE2, etc.) __SE1_____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

_____No_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO- please indicate as such)

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-297 Coreg (carvedilol)

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Protocol 105517/287 (MF447/SB287)

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

__Same as #2(c)_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # [redacted] YES /_X_/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

/S/ 10/31/01

_____ _____
Signature Date
Title:_____

/S/ 11/1/01

_____ _____
Signature of Office/ Date
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 020297
Trade Name: COREG
Generic Name: CARVEDILOL
Supplement Number. 007 **Supplement Type**: SE1
Dosage Form:
Regulatory Action: AE **Action Date**: 8/31/01
COMIS Indication: MANAGEMENT OF ESSENTIAL HYPERTENSION

Indication #1: Increase survival and to reduce the progression of heart failure.
Label Adequacy: Other - see comments
Formulation Needed: No new formulation is needed
Comments (if any) This a revised indication for one they already have - they are now seeking a mortality claim for CHF. They have been issued a pediatric written request for CHF and are conducting studies.

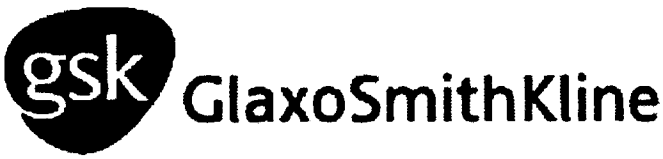
Lower Range	Upper Range	Status	Date
1 months	16 years	Deferred	10/3/04

Comments: Already conducting studies for original application.

This page was last edited on 6/6/01

Signature /S/

Date 10/18/01



NDA 20-297 (S-007)

Coreg® (carvedilol) Tablets

Item 16. Debarment Statement Certification

Item 16. Debarment Statement Certification

Pursuant to Section 306(K)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that the applicant did not and will not use in any capacity, in connection with this application, the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	Please see attached.	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
David E. Wheadon, M.D.	Senior Vice President US Regulatory Affairs
FIRM/ORGANIZATION SmithKline Beecham Corporation	
SIGNATURE David E Wheadon MD	DATE June 4, 2001

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Redacted 1

pages of trade secret and/or confidential commercial information

RHPM Overview of NDA 20-297/S-007
Coreg (carvedilol) Tablets
October 16, 2001

Sponsor: **GlaxoSmithKline**
Type: **6P**
Receipt Date: **March 2, 2001**
User Fee Goal Date: **September 2, 2001**
AE Letter Issued: **August 31, 2001**
Final Draft Labeling: **Received October 3, 2001**

Background
The original carvedilol application was approved on September 14, 1995 for treatment of hypertension and supplement 001 was approved on May 29, 1997 for treatment of congestive heart failure (CHF). This supplemental application was submitted on March 2, 2001 for the treatment of severe CHF. GlaxoSmithKline requested and obtained a priority review in accordance with the unmet medical need for severe heart failure patients. This application consisted of one study, COPERNICUS that evaluated the effect of a single dosing strategy for carvedilol versus placebo on all-cause mortality in subjects with severe heart failure. Other than the Medical/Statistical review, no other reviews were done nor needed.

Medical/Statistical Review
In their joint review, dated June 7, 2001, Drs Stockbridge and Hung concluded that, "the mortality effects, disparate as they are, have been confirmed and that the indications for carvedilol should acknowledge this action. The description of the COPERNICUS effects on mortality plus hospitalization should be described in the results of the study, but with language that says that delaying hospitalization did not result in more days alive and unhospitalized. Effects on hospitalization should not be part of the indications for the use of carvedilol in heart failure. Failure of COPERNICUS to demonstrate even a trend for carvedilol to increase the time to worsening heart failure should result in the elimination of this existing claim."

Financial Disclosure is addressed on page 7 of the medical/statistical review.

Dr. Stockbridge has reviewed the near final labeling submitted on October 3, 2001 and filed a memo with his changes/remarks. The memo is under the Group Leader's memo tab.

DSI
The rationale for no DSI audit is stated in the medical/statistical review on page 7. It states that, "because this was a large multi-center study for which no center contributed a substantial fraction of the subjects, a decision was made not to perform any audits of the clinical sites."

Pediatric Rule
In their cover letter, GlaxoSmithKline states that their study of heart failure in pediatric patients is currently being evaluated under investigator sponsored IND[ ]. The pediatric requirement for this application is deferred since the firm is in the process of conducting the studies.

Near Final Labeling:
I have reviewed the labeling compared to the labeling included with the approvable letter and have marked changes. My marked labeling is attached to the action package along with the a copy of the ODEs previous version.

CSO Summary
To my knowledge there are no issues that would prevent action on this application.

/S/
Zelda McDonald, RHPM

RHPM Overview of NDA 20-297/S-007
Coreg (carvedilol) Tablets
June 15, 2001

Sponsor: **GlaxoSmithKline**
Type: **6P**
Receipt Date: **March 2, 2001**
User Fee Goal Date: **September 2, 2001**

Background
The original carvedilol application was approved on September 14, 1995 for treatment of hypertension and supplement 001 was approved on May 29, 1997 for treatment of congestive heart failure (CHF). This supplemental application was submitted on March 2, 2001 for the treatment of severe CHF. GlaxoSmithKline requested and obtained a priority review in accordance with the unmet medical need for severe heart failure patients. This application consisted of one study, COPERNICUS that evaluated the effect of a single dosing strategy for carvedilol versus placebo on all-cause mortality in subjects with severe heart failure. Other than the Medical/Statistical review, no other reviews were done nor needed.

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Financial Disclosure is addressed on page 7 of the medical/statistical review.

The Division's mark-up of the labeling is appended to the medical/statistical review.

DSI
The rationale for no DSI audit is stated in the medical/statistical review on page 7. It states that, "because this was a large multi-center study for which no center contributed a substantial fraction of the subjects, a decision was made not to perform any audits of the clinical sites."

Pediatric Rule
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CSO Summary
To my knowledge there are no issues that would prevent action on this application.

/S/
Zelda McDonald, RHPM

Meeting Minutes

NDA:	20-297/S-007
Drug:	Coreg (carvedilol) Tablets
Sponsor:	GlaxoSmithKline
Date Requested:	August 31, 2001
Date Confirmation Faxed:	September 17, 2001
Type:	Labeling
Classification:	C
Meeting Date:	September 19, 2001
Meeting Chair:	Robert Temple, M.D.
Meeting Recorder:	Zelda McDonald
External Participant Lead:	Milton Packer, M.D.

FDA:

Robert Temple, M.D.	Director, Office of Drug Evaluation I, HFD-101
Raymond Lipicky, M.D.	Director, Div. of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
James Hung, Ph.D.	Team Leader, Statistics, HFD-710
Andrew Haffer	Regulatory Review Officer, HFD-42
Zelda McDonald	RHPM, HFD-110

GlaxoSmithKline (GSK):

Neil Shusterman, M.D.	Vice President, Cardiovascular Therapeutic Area, NAMA
Mary Ann Lukas, M.D.	Director, cardiovascular Therapeutic Area
Catherine Clark	Director, North American Regulatory Affairs
Milton Packer, M.D.	Chief, Division of circulatory Physiology Columbia University College of Physicians and Surgeons

Background:

NDA 20-297 Supplement 007, for Coreg (carvedilol) tablets, was received by the Agency on March 2, 2001, for the new use of carvedilol in severe heart failure. An approvable letter with marked-up labeling issued on August 31, 2001. GSK reviewed the letter and labeling and were in general agreement with the labeling proposed by the Agency. The purpose of this meeting was to discuss three areas of the labeling: 1) the effect of carvedilol on the risk of hospitalization in the COPERNICUS trial, 2) the indication and 3) the severity of the patient population in the trial.

Meeting:
The following table reflects the revisions GSK made to the table in the labeling the Agency sent with the approvable letter under CLINICAL TRIALS/Congestive Heart Failure.

Table 1. Secondary Endpoint Results of COPERNICUS

~~End point~~		~~Placebo N = 1133~~	~~Carvedilol N=1156~~	~~Hazard ratio (95% CI)~~	
~~All cause mortality~~		~~191 (16.9%)~~	~~132 (11.4%)~~	~~0.66 (0.53 0.82)~~	
End point	**Placebo N = 1133**	**Carvedilol N=1156**	**Hazard ratio (95% CI)**	**% Reduction**	**P value**
~~Mortality + CV hospitalization~~		~~403 (35.6)~~	~~314 (27.2)~~	~~0.73 (0.68 0.84)~~	
Mortality + CV hospitalization	395	314	0.73	27	0.00002
~~Mortality + all hospitalization~~		~~510 (45.0)~~	~~437 (37.8)~~	~~0.79 (0.70 0.90)~~	
Mortality + all hospitalization	507	425	0.76	24	0.00004
Mortality + CHF hospitalization	357	271	0.69	31	0.000004

- The Agency preferred the original table. The Agency believed omitting all cause mortality from the table (even thought it was in the text) was not a good idea. The Agency suggested including "all cause mortality", "mortality + all hospitalization" and "mortality + CHF hospitalization." It would be acceptable to include "mortality +CV hospitalization" as well if GSK felt strongly about it. GSK should keep the text p-value of .0014 but include a nominal p-value in the table and state that it is not adjusted. In addition the confidence intervals should be included as in the original format.

- The Agency stated that the subsection, Subjective Measures" in the CLINICAL TRIALS/Congestive Heart Failure section should be removed or GSK should provide information to justify the inclusion of these data in the label.

- The Agency agreed that the following revisions to the INDICATIONS AND USAGE section were acceptable, reflecting the fact that there was an effect on both mortality and risk of hospitalization, not just the combination.

INDICATIONS AND USAGE
Congestive Heart Failure
Coreg is indicated for the treatment of mild to severe heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitor, and digitalis, to increase survival and also to reduce the risk of hospitalization. *Coreg* may be used in patients unable to tolerate an ACE inhibitor and may also be used in patients who are or are not receiving digitalis, hydralazine or nitrate therapy~~increase time to hospitalization~~.

- Under PRECAUTIONS/General, the Agency removed the following sentence in the last sentence of the last paragraph; this conclusion had been added to the clinical trials section:

  However, in diabetic patients, carvedilol reduces the risk of death and the combined risk of death and hospitalization to a similar degree as in patients without diabetes.

- The Agency asked GSK to round off the adverse events in Tables 2 and 3 to the nearest whole numbers.

- All other GSK suggested labeling changes were acceptable.

Action Item:
GSK will make the changes and submit a "near final" label.

Signature minutes preparer: /S/ 10/10/01

Concurrence, Chair: /S/

Drafted: 10/3/01 Finaled: 10/10/01
RD:

Temple	10/9/01
Stockbridge	10/4/01
Hung	10/3/01
Haffer	10/9/01

Minutes of Telecon Meeting

Date of Meeting: April 2, 2001

NDA Number: 20-297/S-007 Coreg (carvedilol)

Meeting Chair: Raymond Lipicky, M.D.

Meeting Participants:

FDA, HFD-110

Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
Daryl Allis, M.S.N., F.N.P.	Regulatory Health Project Manager, HFD-110

GlaxoSmithKline

Craig Metz, Ph.D.	VP, Cardio-Pulmonary-Urogenital Affairs
Catherine Clark	Director, Regulatory Affairs

Background

The original NDA for Coreg (carvedilol) was approved on September 14, 1995 for the treatment of hypertension and the CHF efficacy supplement was approved on May 29, 1997 for the treatment of mild or moderate (NYHA class II or III) heart failure. This supplement is for the treatment of severe heart failure with a mortality claim. The Division recommends that this submission be presented at the Cardiac and Renal Advisory Committee.

Meeting

Dr. Lipicky wanted to discuss taking the results of the COPERNICUS study of Coreg (carvedilol) to the May Cardiac and Renal Advisory Committee. There is no question that carvedilol has a mortality effect. However, the populations in the COPERNICUS study and the earlier U.S. studies are similar, but the results for mortality and disease progression are rather dissimilar.

Therefore, the problem is how to write the indications section. Dr. Lipicky identified three possible scenarios:

1. Carvedilol is indicated for CHF without specifying the benefit
2. Carvedilol is indicated for CHF because it saves lives
3. Carvedilol is indicated for CHF because it saves lives and prevents progression.

The sponsor asked if they could meet with the Division and one of the primary investigators to go over the data without going to the Advisory Committee. Dr. Lipicky said we could meet but this would not include the public and this is something that should be public. This is an academic issue of how to disseminate data/information like these to the public.

The sponsor asked if the Division had definitely decided to take this application to the Advisory Committee. Dr. Lipicky said no. This in an ideal set of data and provides a good opportunity to discuss how to design studies, interpret data, and report findings. He believes we can accomplish this if the forum does not include having to choose options and formulate guidances.

The sponsor asked whether this discussion has to be on the May agenda. Dr. Lipicky said no; it can be discussed any time. There is another Advisory Committee in August 2001.

Conclusion

The Division and the sponsor will schedule a meeting to review the data and discuss residual issues. A decision to go forward with the Advisory Committee will be made at that point.

Meeting Recorder: /S/ 4-13-01

Concurrence, Chair: /S/

cc:
HDF-110/Mathews

Draft:	04/04/01
LoCicero	04/04/01
Stockbridge	04/05/01
Morgenstern	04/05/01
Final:	04/05/01