

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-012**

**CHEMISTRY REVIEW(S)**

**Addendum to CMC Review #2**  
**Date: 16-October 2006**

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<b>NDA Number:</b>	22-012
<b>Submission Type:</b>	Original
<b>Applicant Name:</b>	GlaxoSmithKline
<b>Submission Dates:</b>	22-Sep-2006 & 26-Sep-2006 5-Oct-2006 & 6-Oct-2006
<b>Proprietary Name:</b>	Coreg CR
<b>USAN Name</b>	Carvedilol phosphate
<b>Dosage Form:</b>	Extended-release Capsules
<b>Dosage Strengths:</b>	10, 20, 40 and 80 mg
<b>Proposed Indication:</b>	Treatment of essential hypertension, mild to severe chronic heart failure, and to reduce cardiovascular mortality in clinically stable post-MI and LVD patients
<b>Chemistry Division:</b>	DPA I, ONDQA
<b>CMC Reviewer:</b>	Eugenia Nashed, Ph.D.
<b>PAL:</b>	Kasturi Srinivasachar, Ph.D.
<b>Branch Chief:</b>	Ramesh Sood, Ph.D.

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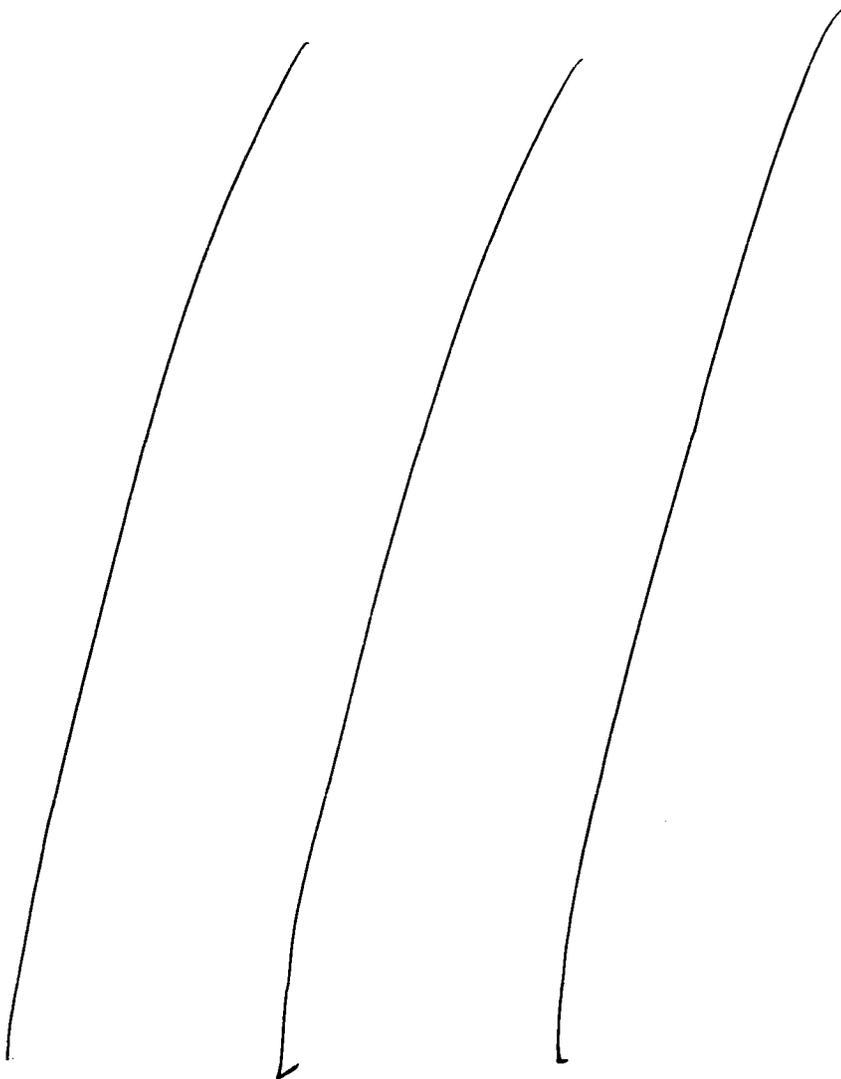
**Recommendations**

The application is recommended for **approval (AP)** from a CMC perspective. All CMC issues are adequately resolved by the applicant and updated drug substance specifications are submitted (see copies attached below). An acceptable (AC) GMP status is available from the Office of Compliance as of October 13, 2006.

The Applicant provided two agreements regarding post-approval stability studies and tightening/review of the acceptance criteria upon manufacturing — batches of the drug product - see submission dated 26-Sep-2006, and CMC rev #2. These agreements should be included in the action letter, as detailed below:

- 1. We remind you of the agreement to address the use of — microparticles in full scale drug product manufacture by conducting additional stability studies as agreed at the September 20, 2006 teleconference and specified in your submission dated September 26, 2006. Please include side-by-side dissolution profiles for the — microparticles and the final drug products manufactured using these microparticles, as discussed during the above referenced teleconference. These stability studies will be performed in addition to the standard stability studies carried on the first three commercial batches of each strength, and the data will be reported in the annual report.*
- 2. We also remind you of the agreement to tighten the acceptance criteria for particle size distribution in the drug substance, residual solvents in the drug substance and microparticles, and drug product dissolution, as warranted by the analysis of data obtained on the first — commercial drug product batches, as agreed at the*

September 20, 2006 teleconference and specified in your submission dated September 26, 2006. The progress of the studies and final tightening of the acceptance criteria, along with the analysis of the results, will be reported via the annual report.



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/s/

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Eugenia Nashed  
10/16/2006 04:37:38 PM  
CHEMIST

Ramesh Sood  
10/16/2006 07:21:02 PM  
CHEMIST

**NDA 22-012**

**Coreg® (carvedilol phosphate) Extended-Release Capsules,  
10, 20, 40 and 80 mg**

**SB Pharmco Puerto Rico Inc. d/b/a GlaxoSmithKline**

**Eugenia M. Nashed, Ph.D.  
Office of New Drug Quality Assessment, Division I**

**Division of Cardiovascular and Renal Drug Products**

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# Chemistry Review Data Sheet

1. NDA 22-012
2. REVIEW #: 2
3. REVIEW DATE: 20-Sep-2006
4. REVIEWER: Eugenia M. Nashed

5. PREVIOUS DOCUMENTS:

<u>Submission(s)</u>	<u>Document Date</u>	<u>Stamp Date</u>	<u>Assigned Date</u>	<u>Reviewed Date</u>
Original NDA	21-Dec-2005	21-Dec-2005	21-Feb-2006	21-Jul-2006; IR letter dated 02-Aug-2006
Amendment BZ	30-June-2006	03-Jul-2006	14-Jul-2006	11-Aug-2006; IR letter dated 11-Aug-2006
Amendment BC	10-July-2006	10-Jul-2006	03-Aug-2006	11-Aug-2006; IR letter dated 11-Aug-2006

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	<u>Stamp Date</u>	<u>Assigned Date</u>
Amendment BC	15-Sep-2006	15-Sep-2006	15-Sep-2006
Amendment BC	20-Sep-2006	20-Sep-2006	20-Sep-2006

7. NAME & ADDRESS OF APPLICANT:

Name: SB Pharmco Puerto Rico Inc. d/b/a GlaxoSmithKline

Address: One Franklin Plaza, 200 N. 16<sup>th</sup> Street, Philadelphia, PA 19102

Representative: Catherine Clark, Director, U.S. Regulatory Affairs

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

Telephone: (215) 751-3868

Fax: (215) 751-4926

### 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Coreg CR
- b) Non-Proprietary Name (USAN): Carvedilol Phosphate Extended-release Capsules
- c) Code Name/# (ONDC only): SK&F-105517-D
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 2
  - Submission Priority: S

### 9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Nonselective  $\beta$ -blockade with  $\alpha_1$ -blocking activity for treatment of essential hypertension, mild to severe chronic heart failure and to reduce mortality in clinically stable survivors of the acute phase of MI.

### 11. DOSAGE FORM: Extended-release Capsules

### 12. STRENGTH/POTENCY: 10, 20, 40 and 80 mg (as carvedilol phosphate)

### 13. ROUTE OF ADMINISTRATION: Oral

### 14. Rx/OTC DISPENSED: Rx OTC

### 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

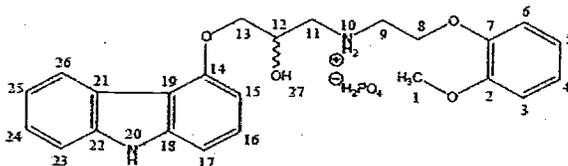
SPOTS product – Form Completed

Not a SPOTS product

### 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet



$C_{24}H_{26}N_2O_4 \cdot H_3PO_4 \cdot \frac{1}{2} H_2O$  M.W. 513.5 g/mol and

1-(9H-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol dihydrogen phosphate

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. Supporting DMFs:

DMF #	TY PE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS <sup>3</sup>
	IV			3	Adequate	12/30/02 & 6/11/03	
	IV			3	Adequate	01/16/04	
	III			1	Adequate	07/27/04	
	III			4	Adequate	LOA and GSK Acceptance Specifications provided in section m3.2.P.7	
	III			4	Adequate	LOA and GSK Acceptance Specifications provided in section m3.2.P.7	
	III			4	Adequate	LOA and GSK Acceptance Specifications provided in section m3.2.P.7	
	III			4	Adequate	LOA and GSK Acceptance Specifications provided in section m3.2.P.7	
	III			4	Adequate	LOA and GSK Acceptance Specifications provided in section m3.2.P.7	
	III			4	Adequate	LOA and GSK Acceptance Specifications provided in section m3.2.P.7	
	III			4	Adequate	LOA and GSK Acceptance Specifications provided in section m3.2.P.7	
	III			4	Adequate	LOA and GSK Acceptance Specifications provided in section m3.2.P.7	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

<sup>3</sup> Include reference to location in most recent CMC review

### B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND 27,114	GSK	Coreg (carvedilol phosphate) Tablets	Pending		Referenced for this NDA
IND 70,154	GSK	Carvedilol Phosphate Micropump Modified Release (MR) Capsules	Pending		Referenced for this NDA
NDA 20-297	GSK	Coreg (carvedilol) Tablets	Approved		On the market, bid IR, the same indication. Referenced for this NDA.

### C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT

### 18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORW'D	STATUS/ REVIEWER	COMMENTS
Biometrics	None			
EES	GMP Inspections	Feb 9, 2006	Pending	5 establishments AC, 1 inspections for drug product manufacturing site (Flamel Tech., France) is pending
Pharm/Tox	Safety	May 23, 2006	Pending	Forwarded by e-mail to Albert Defelice
Biopharm	Dissolution	Feb 6, 2006	Pending Christine Garnett	The applicant did not submit results of full clinical trials for this drug product, only ClinPharm data. The adequacy of the dissolution method and specifications was discussed with ClinPharm team and subsequently the final dissolution specifications were agreed on with the applicant during T-con on sep 20, 2006.
DMETS	Trade name	Jan 31, 2006	Pending	Revisions recommended; IR letter forwarded on Jul 7, 2006.
Methods Validation				Will be initiated, if necessary, upon completion of the review
DDMAC	Labeling	Jan 31, 2006	Aug 9, 2006, Lisa Hubbard	Revisions to the labeling are recommended.
EA	None			Exception requested and granted (see CMC Rev #1)
Microbiology	None			Non-sterile



# The Chemistry Review for NDA 22-012

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application is recommended for approval (AP) from a CMC perspective, provided that an acceptable (AC) GMP status is available for drug product manufacturing facility at Flamel Technologies, Pessac, France.

- CMC comments forwarded to the applicant in IR letters dated Aug 2, and Aug 11, 2006, were adequately addressed by the applicant. See further down in this review, a point by point evaluation of the provided responses and data.
- The EER for this NDA is pending. AC status is currently available for all establishments, except drug product manufacturing facility at Flamel Technologies in Pessac, France. — An acceptable GMP status is needed for all manufacturing and testing facilities before the approval.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

- No Phase 4 commitments are recommended.
- The applicant agreed to review specifications for drug product dissolution, content of residual solvents and particle size distribution in the drug substance, upon manufacturing of — batches of drug product. The acceptance criteria for the above attributes will be tightened as warranted by the results.
- The applicant provided an agreement to conduct additional stability studies on a full-scale to-be-marketed drug product batches to support the —, and to address changes in drug product dissolution occurring upon storage (especially at accelerated conditions) and differences in dissolution profiles observed for biobatches, stability (pilot scale), and full scale batches (new building at Flamel Technologies).

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Executive Summary Section

The drug substance, carvedilol phosphate hemihydrate is a new salt form of carvedilol (free base) which has been marketed for several years in the immediate release Coreg Tablets under NDA 20-297. The applicant has developed a new extended-release formulation for once-daily dosing. Four strengths of drug product (10, 20, 40 and 80 mg, expressed as carvedilol phosphate), are projected for marketing to provide similar 24 hours exposure levels of carvedilol, as the currently marketed twice-daily immediate release Coreg tablets (3.125, 6.25, 12.5 and 25 mg respectively).

Drug substance

The drug substance, carvedilol phosphate, is a white solid and possesses one chiral center. Although some data were presented to indicate that the biological activity of S stereoisomer is different from the R stereoisomer, the drug is being developed as a racemate.

The hemihydrate form was selected for development due to

The drug substance is manufactured by SmithKline Beecham in Cork, Ireland,

Drug Product

The drug product is manufactured as a hard gelatin capsules in 4 different sizes and 4 different color combinations (white-green, white-yellow, yellow-green and white-white), reflecting the 4 strengths of the drug product, 10, 20, 40 and 80 mg. Each capsule is filled with microparticles:

In addition to the microparticles, the capsules contain magnesium stearate \_\_\_\_\_  
Other excipients include \_\_\_\_\_ Hydrogenated Castor Oil \_\_\_\_\_  
\_\_\_\_\_, Methacrylic Acid Copolymers \_\_\_\_\_  
\_\_\_\_\_ and Hydrogenated Vegetable Oil \_\_\_\_\_

The compatibility studies between  
the drug substance and excipients were carried out and revealed that \_\_\_\_\_  
Hydrogenated Castor Oil \_\_\_\_\_, is causing degradation of the drug substance by  
forming a potentially genotoxic impurity (preliminary evaluation by PharmTox team), \_\_\_\_\_

The manufacture and testing of microparticles is carried by a contract facility Flamel  
Technologies in France. The drug product capsules \_\_\_\_\_, are filled with  
microparticles by SKB at Crawley, UK.

#### B. Description of How the Drug Product is Intended to be Used

The drug product, Coreg (carvedilol phosphate) Extended-release Capsules, 10 mg, 20 mg, 40  
mg, and 80 mg, are to be used orally once-daily for treatment of essential hypertension, mild to  
severe chronic heart failure and to reduce mortality in clinically stable survivors of the acute  
phase of MI. The proposed dosage is up to 80 mg once-daily.

The drug product is recommended for storage in \_\_\_\_\_ at  
room temperature. The applicant has requested expiry period of 24 months for the final drug  
product capsules \_\_\_\_\_

\_\_\_\_\_ The request is supported by stability  
data on pilot scale batches and an agreement for additional stability studies conducted on full  
scale batches, as discussed during teleconference with applicant on Sep 20, 2006.

#### C. Basis for Approvability or Not-Approval Recommendation

Based on the extensive information and data provided in this application, an **approval (AP)** is  
recommended from a CMC perspective, provided that acceptable GMP status is available from  
the Office of Compliance for all manufacturing and testing facilities supporting this application.  
The EER for this NDA is currently pending. As of Sep 20, 2006, an AC status is available for all  
establishments, except for drug product manufacturing facility at Flamel Technologies, Pessac,  
France (manufacture of microparticles, \_\_\_\_\_)

**Executive Summary Section**

The original NDA application was reviewed and an IR letter dated Aug 2, 2006, was forwarded to the applicant based on the draft CMC review dated Jul 21, 2006.

Upon the conclusion of the draft CMC review an amendment dated Jun 30, 2006, was submitted based on the agreement negotiated by the applicant during the pre-NDA meeting on Jun 15, 2005. The amendment contained updated stability data ( — at label conditions) for the primary stability batches manufactured with a pilot scale microparticles (m3.2.P.8.1), and comparative data for drug product batches manufactured with a full production-scale microparticles (m3.2.P.5.4). Also, an updated specification sheet for drug substance was submitted with changes proposed to the acceptance criteria for particle size distribution and — (m3.2.S.4.1 and m3.2.S.4.5). In addition, a new data on complete dissolution profiles collected at — pH for the full-scale batches manufactured at the new manufacturing facility at Flamel Technologies, as compared to the dissolution of the pivotal clinical batches, were submitted to fulfill the EOP 2 agreement (Sep 22, 2004) with the BioPharm Team. Also, a brief update on the — was submitted on Jul 10, 2006, in response to our request for clarification. Both amendments were reviewed (see revised CMC Review #1 dated Aug 11, 2006) and IR letter dated August 11, 2006, was forwarded to the applicant.

The applicant provided partial responses to both IR letters by several e-mails to the PM, and confirmed that the responses provided by e-mail will be identical to those submitted electronically to the NDA. Upon review of the e-mail responses, two teleconferences discussing drug product **dissolution** (bio-batches, stability/pilot and full scale batches), **residual solvents**, **particle size distribution** in drug substance and —, were held with the applicant on Sep 15, and Sep 20, 2006. The applicant agreed to submit an electronic response to the IR letters dated Aug 2, and 11, 2006, and confirmed that the response will be identical to all responses provided by prior e-mails and also will reflect the discussion and agreements reached during teleconferences on Sep 15 and 20, 2006.

See further down in this review, a point by point evaluation of applicant's responses to each comment. The CMC comments reminding about the post-approval agreements provided by the applicant are summarized at the end of this review and should be included in the action letter.

**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

Chemist Name/Date: Same date as draft review  
Chemistry Team Leader Name/Date  
Project Manager Name/Date

**C. CC Block**

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/s/

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Eugenia Nashed  
9/25/2006 12:09:43 PM  
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Ramesh Sood  
9/25/2006 12:35:53 PM  
CHEMIST

**NDA 22-012**

**Coreg® (carvedilol phosphate) Extended-Release Capsules,  
10, 20, 40 and 80 mg  
(containing carvedilol phosphate hemihydrate)**

**SB Pharmco Puerto Rico Inc. d/b/a GlaxoSmithKline**

**Eugenia M. Nashed, Ph.D.  
Office of New Drug Quality Assessment, Division I**

**Division of Cardiovascular and Renal Drug Products**

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# Chemistry Review Data Sheet

1. NDA 22-012
2. REVIEW #: 1
3. REVIEW DATE: 11-Aug-2006
4. REVIEWER: Eugenia M. Nashed
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	<u>Stamp Date</u>	<u>Assigned Date</u>
Original NDA	21-Dec-2005	21-Dec-2005	21-Feb-2006
Amendment BZ	30-June-2006	03-Jul-2006	14-Jul-2006
Amendment BC	10-July-2006	10-Jul-2006	03-Aug-2006

7. NAME & ADDRESS OF APPLICANT:

Name: SB Pharmco Puerto Rico Inc. d/b/a GlaxoSmithKline

Address: One Franklin Plaza, 200 N. 16<sup>th</sup> Street, Philadelphia, PA 19102

Representative: Catherine Clark, Director, U.S. Regulatory Affairs

Telephone: (215) 751-3868

Fax: (215) 751-4926

8. DRUG PRODUCT NAME/CODE/TYPE:



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

- a) Proprietary Name: Coreg CR  
 b) Non-Proprietary Name (USAN): Carvedilol Phosphate Extended-release Capsules  
 c) Code Name/# (ONDC only): SK&F-105517-D  
 d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 2
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Nonselective  $\beta$ -blockade with  $\alpha_1$ -blocking activity for treatment of essential hypertension, mild to severe chronic heart failure and to reduce mortality in clinically stable survivors of the acute phase of MI.

11. DOSAGE FORM: Extended-release Capsules

12. STRENGTH/POTENCY: 10, 20, 40 and 80 mg (as carvedilol phosphate)

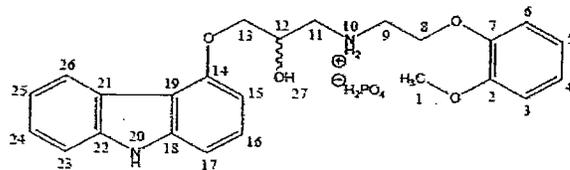
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):  
 SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



$C_{24}H_{26}N_2O_4 \cdot H_3PO_4 \cdot \frac{1}{2} H_2O$  M.W. 513.5 g/mol and

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

1-(9H-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol dihydrogen phosphate

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. Supporting DMFs:

DMF #	TY PE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS <sup>3</sup>
	IV			3	Adequate	12/30/02 & 6/11/03	
	IV			3	Adequate	01/16/04	
	III			1	Adequate	07/27/04	
	III			4	Adequate	LOA and GSK Acceptance Specifications provided in section m3.2.P.7	
	III			4	Adequate	LOA and GSK Acceptance Specifications provided in section m3.2.P.7	
	III			4	Adequate	LOA and GSK Acceptance Specifications provided in section m3.2.P.7	
	III			4	Adequate	LOA and GSK Acceptance Specifications provided in section m3.2.P.7	
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	III			4	Adequate	LOA and GSK Acceptance Specifications provided in section m3.2.P.7	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

<sup>3</sup> Include reference to location in most recent CMC review

#### B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND	GSK	Coreg (carvedilol phosphate)	Pending		Referenced for this NDA

**Chemistry Review Data Sheet**

27,114		Tablets		
IND 70,154	GSK	Carvedilol Phosphate Micropump Modified Release (MR) Capsules	Pending	Referenced for this NDA
NDA 20-297	GSK	Coreg (carvedilol) Tablets	Approved	On the market, bid IR, the same indication. Referenced for this NDA.

**C. Related Documents:**

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT

**18. CONSULTS/CMC-RELATED REVIEWS:**

CONSULTS	SUBJECT	DATE FORW'D	STATUS/ REVIEWER	COMMENTS
Biometrics	None			
EES	GMP Inspections	Feb 9, 2006	Pending	4 establishments AC, 2 inspections for drug product manufacturing sites (UK and France) are pending
Pharm/Tox	Safety	May 23, 2006	Pending	Forwarded by e-mail to Albert Defelice
Biopharm	Dissolution	Feb 6, 2006	Pending	Biopharm Team will evaluate adequacy of the selected method and time points/specifications – per conversation with Christine Garnett on June 6, 2006.
DMETS	Trade name	Jan 31, 2006	Pending	Revisions recommended; IR letter forwarded on Jul 7, 2006.
Methods Validation				Will be initiated upon completion of the review
DDMAC	Labeling	Jan 31, 2006	Aug 9, 2006, Lisa Hubbard	Revisions to the labeling are recommended.
EA	None			Exception requested
Microbiology	None			

# The Chemistry Review for NDA 22-012

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application is considered to be **approvable (AE)** from a CMC perspective.

- Comments forwarded to the applicant in IR letters dated Aug 2, and Aug 11, 2006, need to be adequately addressed prior to the approval of the application.
- The EER for this NDA is currently pending. AC status is currently available for all establishments, except drug product manufacturing facilities at Crawley, UK (GSK) and Flamel Technologies in Pessac, France. An acceptable GMP status will be needed for all manufacturing and testing facilities before the approval.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None recommended at this time.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, carvedilol phosphate hemihydrate is a new salt form of carvedilol (free base) which has been marketed for several years in the immediate release Coreg Tablets under NDA 20-297. The applicant has developed a new Extended-release formulation for once-daily dosing. Four strengths of drug product (10, 20, 40 and 80 mg, expressed as carvedilol) are projected for marketing to provide similar 24 hours exposure levels of carvedilol, as the currently marketed twice-daily immediate release Coreg tablets (3.125, 6.25, 12.5 and 25 mg respectively).

#### Drug substance

The drug substance, carvedilol phosphate hemihydrate, is a white solid and possesses one chiral center. Although some data were presented to indicate that the biological activity of S stereoisomer is different from the R stereoisomer, the drug is being developed as a racemate.

was selected for development

The hemihydrate form

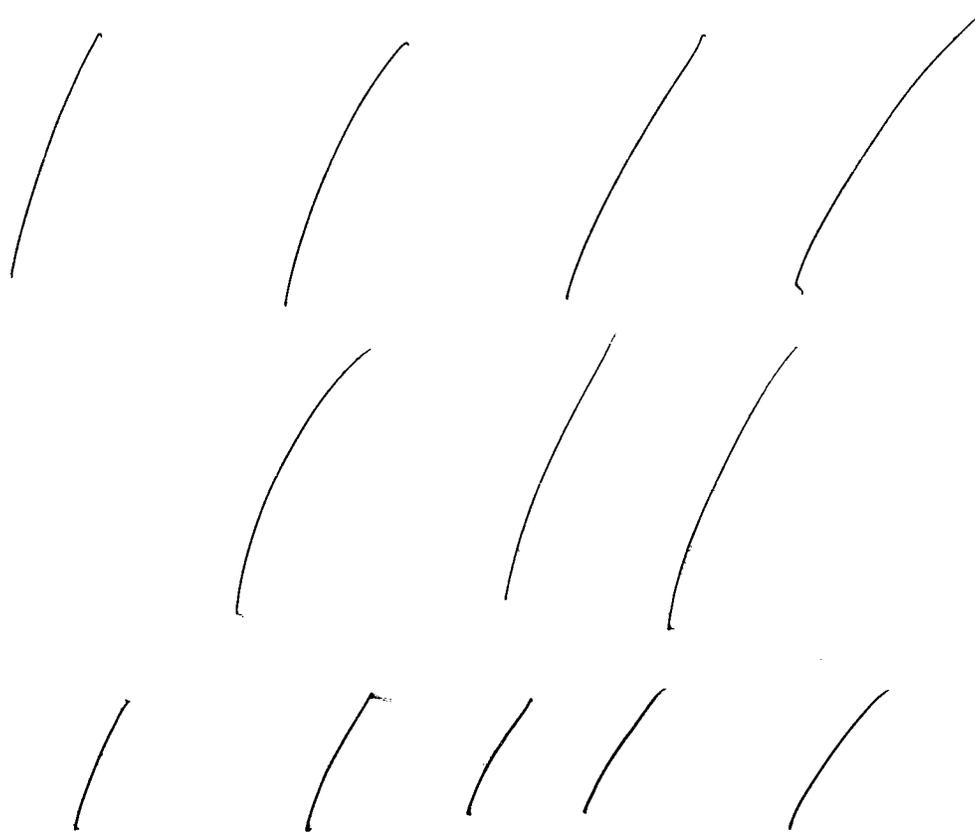


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The drug substance is manufactured by SmithKline Beecham in Cork, Ireland,

Drug Product

The drug product is manufactured as a hard gelatin capsules in 4 different sizes and 4 different color combinations (white-green, white-yellow, yellow-green and white-white), reflecting the 4 strengths of the drug product, 10, 20, 40 and 80 mg. Each capsule is filled with \_\_\_\_\_ microparticles:



In addition to the microparticles, the capsules contain magnesium stearate \_\_\_\_\_

Other excipients include \_\_\_\_\_

Hydrogenated Castor Oil \_\_\_\_\_

Methacrylic Acid Copolymers \_\_\_\_\_

and Hydrogenated Vegetable Oil \_\_\_\_\_

The compatibility studies between the drug substance and excipients were carried out and revealed that \_\_\_\_\_ Hydrogenated Castor Oil \_\_\_\_\_ is causing degradation of the drug substance by forming a potentially genotoxic impurity (preliminary evaluation by PharmTox team).

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The manufacture and testing of microparticles is carried by a contract facility Flamel Technologies in France. The drug product capsules / \_\_\_\_\_ are filled with microparticles by SKB at Crawley, UK.

**B. Description of How the Drug Product is Intended to be Used**

The drug product, Coreg (carvedilol phosphate hemihydrate) Extended Release Capsules, 10 mg, 20 mg, 40 mg, and 80 mg, are to be used orally once-daily for treatment of essential hypertension, mild to severe chronic heart failure and to reduce mortality in clinically stable survivors of the acute phase of MI. The proposed dosage is up to 80 mg once-daily.

The drug product is recommended for storage in \_\_\_\_\_ at room temperature. The applicant has requested expiry period of 24 months for the final drug product capsules \_\_\_\_\_ See our comments in IR letter dated Aug 2, 2006.

**C. Basis for Approvability or Not-Approval Recommendation**

Based on the extensive information and data provided in this submission, the application is considered to be **approvable**, from a CMC perspective. The approval will be recommended when the applicant addresses adequately all deficiency comments outlined in IR letters dated Aug 2, and Aug 11, 2006, and when an acceptable (AC) GMP status is recommended for all manufacturing and testing facilities supporting this application. The EER for this NDA is currently pending. As of August 10, 2006, an AC status is available for all establishments, except drug product manufacturing facilities at Crawley, UK (capsule fill by GSK, inspection performed) and Flamel Technologies in Pessac, France (manufacture of microparticles, \_\_\_\_\_).

The original NDA application was reviewed and an IR letter dated Aug 2, 2006, was forwarded to the applicant based on the draft CMC review dated Jul 21, 2006.

Upon the conclusion of the draft review an amendment dated Jun 30, 2006, was submitted based on the agreement negotiated by the applicant during pre-NDA meeting on Jun 15, 2005. The amendment contained updated stability data ( \_\_\_\_\_ at label conditions) for the primary stability batches manufactured with a pilot scale microparticles (m3.2.P.8.1), and comparative data for drug product batches manufactured with a full production-scale microparticles (m3.2.P.5.4). Also, an updated specification sheet for drug substance was submitted with changes proposed to the acceptance criteria for particle size distribution and \_\_\_\_\_ (m3.2.S.4.1 and m3.2.S.4.5). In addition, a new data on complete dissolution profiles collected at four different pH for the full-scale batches manufactured at the new manufacturing facility at Flamel Technologies, as compared to the dissolution of the pivotal clinical batches, were submitted to fulfill the EOP 2 agreement (Sep 22, 2004) with the BioPharm Team. Also, a brief update on the \_\_\_\_\_ was submitted on Jul 10, 2006, in response to our request for

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clarification. Both amendments were reviewed and IR letter dated August 11, 2006, was forwarded to the applicant.

All submissions received prior to August 10, 2006, are reflected in this combined review. See below, a summary of the more important CMC deficiencies remaining to be addressed by the applicant.

**Inadequate Controls for Drug Substance.**

The applicant needs to submit specification sheet for the \_\_\_\_\_, clarify the manufacturing procedure regarding the \_\_\_\_\_

Also, drug substance specification sheet needs to be revised to include individual method numbers, assure adequate monitoring of the hemihydrate form during release and stability, upgrade the acceptance criteria for particle size distribution and limit the content of residual solvents. In addition, a removal of the proposed \_\_\_\_\_ testing is strongly recommend, since this is the only quantitative test for the \_\_\_\_\_

**New, Possibly Genotoxic Impurity Formed by Reaction of API with Excipients.**

The applicant reported formation of \_\_\_\_\_ in the drug product due to the reaction of drug substance with \_\_\_\_\_ hydrogenated castor oil used as \_\_\_\_\_. This impurity is reaching \_\_\_\_\_ in the drug product after storage for \_\_\_\_\_ at the accelerated conditions. \_\_\_\_\_ was predicted to be genotoxic in two or more *in vitro* and *in vivo* genotox assays, based on the preliminary Computational Toxicology Report by the PharmTox team, dated Jun 23, 2006. The final evaluation by Albert Defelice is pending.

**Unacceptably high level of residual solvents in the drug product.**

The currently proposed specification for the content of residual \_\_\_\_\_ in the drug product microparticles is NMT \_\_\_\_\_. This, combined with relatively high levels of residual \_\_\_\_\_ carried over from drug substance (proposed specifications for drug substance: NMT \_\_\_\_\_) is unacceptably high and does not reflect the process capabilities or the submitted data (up to \_\_\_\_\_).

**Revision of the requested expiry period or submission of additional data.**

24 months expiry period was requested for the final drug product capsules, \_\_\_\_\_.  
\_\_\_\_\_. Currently submitted data seem to support the requested 24 months expiry periods for the pilot scale drug product capsules. \_\_\_\_\_

\_\_\_\_\_. The submitted stability data for pilot batches include \_\_\_\_\_ storage at the label conditions and



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For a full list of CMC deficiency comments refer to IR letters dated Aug 2, and Aug 11, 2006, that were forwarded to the applicant. Also, they summarized at the end of this review.

**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

Chemist Name/Date: Same date as draft review  
Chemistry Team Leader Name/Date  
Project Manager Name/Date

**C. CC Block**

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Ramesh Sood  
8/14/2006 03:34:52 PM  
CHEMIST

Initial Quality Assessment  
Branch I

OND Division: Division of Cardiovascular and Renal Products  
NDA: 22-012  
Applicant: GlaxoSmithKline  
Letter Date: 21 December 2005  
Stamp Date: 21 December 2005  
PDUFA Date: 21 October 2006  
Tradename: Coreg CR  
Established Name: carvedilol phosphate  
Dosage Form: Controlled Release Capsules 10,20, 40 and 80 mg  
(expressed as carvedilol phosphate)  
Route of Administration: Oral  
Indication: Treatment of essential hypertension, mild to severe  
chronic heart failure and to reduce mortality in  
clinically stable survivors of the acute phase of a  
MI  
Assessed by: Kasturi Srinivasachar, Ph.D.

Summary

Carvedilol phosphate is a new salt form of carvedilol (free base) which has been marketed for a number of years as Coreg Tablets (NDA 20-297), an immediate release formulation. GSK has developed a new controlled release formulation using carvedilol phosphate hemihydrate as the drug substance for once daily dosing. Coreg CR capsules strengths of 10, 20, 40 and 80 mg were chosen to provide similar exposure levels of carvedilol over a 24 hr period as achieved by BID administration of Coreg tablet strengths of 3.125, 6.25, 12.5 and 25 mg respectively. The main advantage claimed for this new formulation is that it simplifies the medication regimen for the intended patient population which typically is on 6-7 daily drugs and hence enhances compliance. The Applicant has had CMC specific meetings with the Division chemists at EOP2 and pre-NDA stages and minutes from these are in DFS.

Drug Substance

The drug substance, carvedilol phosphate hemihydrate is a white to almost- white solid and possesses one stereogenic center. Hence, there are 2 enantiomers; however, the drug substance for this NDA is being developed as a racemate.

The hemihydrate was chosen for development because

The drug substance is manufactured by SmithKline Beecham in Cork, Ireland

approved NDA 20-297 for Coreg tablets, all cmc information for this compound is by reference to this application.

Drug Product

Coreg controlled release capsules will be available in 4 strengths of 10, 20, 40 and 80 mg. The capsules are filled with \_\_\_\_\_ microparticles—drug layered immediate release particles and \_\_\_\_\_ controlled release microparticles that are drug layered and the coated with \_\_\_\_\_ methacrylic acid copolymer \_\_\_\_\_

\_\_\_\_\_ The capsules contain a mixture of these \_\_\_\_\_ in an active drug content ratio of \_\_\_\_\_ for all strengths. In addition to these microparticles the capsules contain magnesium stearate \_\_\_\_\_ Common excipients are used in the manufacture of the drug product and an excipient compatibility study has been carried out. \_\_\_\_\_ microparticles are composed of \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Manufacture of Coreg CR capsules is carried out by SmithKline Beecham at Crawley, West Sussex. UK. There is also a contract facility, Flamel Technologies, France, for the manufacture, testing and bulk packaging of the IR and \_\_\_\_\_ microparticles \_\_\_\_\_

\_\_\_\_\_ Coreg capsules are packaged in \_\_\_\_\_  
\_\_\_\_\_ Primary stability data \_\_\_\_\_

\_\_\_\_\_ ) from batches of 10mg and 80 mg strengths (intermediate strengths have been bracketed), manufactured at pilot scale, and packaged in \_\_\_\_\_ ; have been submitted. Additional data will be provided within 6.5 months of NDA submission, as agreed to in the pre-NDA meeting.

Critical Issues for Review

Drug substance

- \_\_\_\_\_
- Particle size of the drug substance has been the topic of discussion in meetings with the Applicant – whether a particle size specification is needed and if it is what it should be based on. The Applicant still has not fully resolved this issue and has set only a \_\_\_\_\_, value at this stage with the commitment to set a \_\_\_\_\_ limit after additional batch analysis.
- \_\_\_\_\_
- A limit of NMT \_\_\_\_\_, has been proposed for residual \_\_\_\_\_ in the DS specifications which needs adequate justification to be acceptable.

Drug Product

- This is a controlled release product and all aspects of product manufacturing, raw material and finished product controls are important. Properties of the release controlling excipients and drug substance characteristics which are relevant to product performance are critical.
- Dissolution specifications are critical. Although OCPB will be primarily responsible for the dissolution specifications for the final product, the ONDQA reviewer needs to be involved in this as well, especially those aspects not reviewed by OCPB e.g. stability, in process controls etc.
- Process scale up by \_\_\_\_\_ is planned for commercial batches. In the pre-NDA meeting, GSK stated that changes to the process in connection with this scale up would be "minor". They were requested to provide full details of the changes and a side-by-side comparison with the process used for pivotal clinical batches.
- The \_\_\_\_\_ microparticles are manufactured at a separate contract facility. Data to support \_\_\_\_\_ proposed should be evaluated.
- \_\_\_\_\_ is used in the formulation. This excipient has had toxicity problems in \_\_\_\_\_ It may be safe in an oral dosage form especially since the amounts are small but this needs to be confirmed.
- \_\_\_\_\_ is used in the manufacturing process and \_\_\_\_\_ microparticles have specifications for residual \_\_\_\_\_ of NMT \_\_\_\_\_. The Applicant states that compliance with this limit makes final product testing unnecessary based on the ICH Q3C Guidance.

Comments and Recommendation:

The NDA is fileable from a CMC perspective. This NDA should be reviewed by a single reviewer, ideally a senior member from Branch I who has some experience with modified release products. Dr Gurpreet Gill-Sangha would be good choice since the reviewer who participated in the IND phases is now in post-marketing. Informal consultation with Dr Robert Liu, who has academic experience in modified release dosage forms is recommended.

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Kasturi Srinivasachar  
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