

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-012

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

22-012

NAME OF APPLICANT / NDA HOLDER

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

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Coreg CR

ACTIVE INGREDIENT(S)

Carvedilol phosphate

STRENGTH(S)

10 mg Carvedilol phosphate

20 mg Carvedilol phosphate

40 mg Carvedilol phosphate

80 mg Carvedilol phosphate

DOSAGE FORM

Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
4,503,067

b. Issue Date of Patent
3/5/1985

c. Expiration Date of Patent
3/5/2007

d. Name of Patent Owner
Roche Diagnostics GmbH

Address (of Patent Owner)
Sandhofer Strasse 116

City/State
Mannheim, Germany

ZIP Code
D-683

FAX Number (if available)
011 49 621 759 28 90

Telephone Number
011 49 621 759-0

E-Mail Address (if available)
www.roche-diagnostics.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)
GlaxoSmithKline - UW2220
709 Swedeland Road, P.O. Box 1539

City/State
King of Prussia, PA

ZIP Code
19406-0939

FAX Number (if available)
610-270-5090

Charles M. Kinzig, Esq.
Vice President, Corporate Intellectual Property

Telephone Number
610-270-5021

E-Mail Address (if available)
charles.m.kinzig@gsk.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2	Patent Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
13		<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Treatment of hypertension	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Mary E. McCarthy

December 12, 2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Mary E. McCarthy

Address
GlaxoSmithKline
709 Swedeland Road-UW2220
P.O. Box 1539

City/State
King of Prussia, PA

ZIP Code
19406-09392

Telephone Number
610-270-5022

FAX Number (if available)
610-270-5090

E-Mail Address (if available)
mary.e.mccarthy@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtm/fdahtm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

4. Method of Use (continued)

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information.

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) 15	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
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4.2a If the answer to 4.2 is "Yes," identify the use with specificity the use with reference to the proposed labeling for the drug product.

Use (Submit indication or method of use information as identified specifically in the approved labeling.)

Treatment of hypertension

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
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22-012

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d/b/a/ GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Coreg CR

ACTIVE INGREDIENT(S)

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STRENGTH(S)

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40 mg Carvedilol phosphate
80 mg Carvedilol phosphate

DOSAGE FORM

Capsule

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FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
5,760,069

b. Issue Date of Patent
06/02/1998

c. Expiration Date of Patent
06/07/2015

d. Name of Patent Owner
Roche Diagnostics GmbH

Address (of Patent Owner)
Sandhofer Strasse 116

City/State
Mannheim, Germany

ZIP Code
D-683

FAX Number (if available)
011 49 621 759 28 90

Telephone Number
011 49 621 759-0

E-Mail Address (if available)
www.roche-diagnostics.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)
GlaxoSmithKline – UW2220
709 Swedeland Road, P.O. Box 1539

City/State
King of Prussia, PA

ZIP Code
19406-0939

FAX Number (if available)
610-270-5090

Charles M. Kinzig, Esq.
Vice President, Corporate Intellectual Property

Telephone Number
610-270-5021

E-Mail Address (if available)
charles.m.kinzig@gsk.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) | Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. | Use: (Submit indication or method of use information as identified specifically in the approved labeling.)
 Treatment of mild-to-severe heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitor, and digitalis, to increase survival

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Mary E M McCarthy

December 12, 2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Mary E. McCarthy

Address

GlaxoSmithKline
709 Swedeland Road-UW2220
P.O. Box 1539

City/State

King of Prussia, PA

ZIP Code

19406-09392

Telephone Number

610-270-5022

FAX Number (if available)

610-270-5090

E-Mail Address (if available)

mary.e.mccarthy@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtm/fdahtm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

4. Method of Use (continued)	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information.</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number (as listed in the patent) 6	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify the use with specificity the use with reference to the proposed labeling for the drug product.	<i>Use (Submit indication or method of use information as identified specifically in the approved labeling.)</i> Treatment of mild-to-severe heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitor, and digitalis, to increase survival

4. Method of Use (continued)	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information.</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number (as listed in the patent) 7	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify the use with specificity the use with reference to the proposed labeling for the drug product.	<i>Use (Submit indication or method of use information as identified specifically in the approved labeling.)</i> Treatment of mild-to-severe heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitor, and digitalis, to increase survival

**PATENT INFORMATION SUBMITTED WITH THE
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ACTIVE INGREDIENT(S)

Carvedilol phosphate

STRENGTH(S)

10 mg Carvedilol phosphate
20 mg Carvedilol phosphate
40 mg Carvedilol phosphate
80 mg Carvedilol phosphate

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1. GENERAL

a. United States Patent Number
5,902,821

b. Issue Date of Patent
05/11/1999

c. Expiration Date of Patent
02/07/2016

d. Name of Patent Owner
Roche Diagnostics GmbH

Address (of Patent Owner)
Sandhofer Strasse 116

City/State
Mannheim, Germany

ZIP Code
D-683

FAX Number (if available)
011 49 621 759 28 90

Telephone Number
011 49 621 759-0

E-Mail Address (if available)
www.roche-diagnostics.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

GlaxoSmithKline – UW2220
709 Swedeland Road, P.O. Box 1539

City/State
King of Prussia, PA

ZIP Code
19406-0939

FAX Number (if available)
610-270-5090

Charles M. Kinzig, Esq.
Vice President, Corporate Intellectual Property

Telephone Number
610-270-5021

E-Mail Address (if available)
charles.m.kinzig@gsk.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
 1 Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)
 Treatment of mild-to-severe heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitor, and digitalis, to increase survival

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Mary E McCarthy

December 12, 2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Mary E. McCarthy

Address

GlaxoSmithKline
709 Swedeland Road-UW2220
P.O. Box 1539

City/State

King of Prussia, PA

ZIP Code

19406-09392

Telephone Number

610-270-5022

FAX Number (if available)

610-270-5090

E-Mail Address (if available)

mary.e.mccarthy@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtm/fdahtm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

4. Method of Use (continued)	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information.</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number (as listed in the patent) 3	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify the use with specificity the use with reference to the proposed labeling for the drug product.	Use (Submit indication or method of use information as identified specifically in the approved labeling.) Treatment of mild-to-severe heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitor, and digitalis, to increase survival

4. Method of Use (continued)	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information.</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number (as listed in the patent) 4	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify the use with specificity the use with reference to the proposed labeling for the drug product.	Use (Submit indication or method of use information as identified specifically in the approved labeling.) Treatment of mild-to-severe heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitor, and digitalis, to increase survival

4. Method of Use (continued)	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information.</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number (as listed in the patent) 5	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify the use with specificity the use with reference to the proposed labeling for the drug product.	Use (Submit indication or method of use information as identified specifically in the approved labeling.) Treatment of mild-to-severe heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitor, and digitalis, to increase survival

4. Method of Use (continued)	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information.</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number (as listed in the patent) 6	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify the use with specificity the use with reference to the proposed labeling for the drug product.	Use (Submit indication or method of use information as identified specifically in the approved labeling.) Treatment of mild-to-severe heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitor, and digitalis, to increase survival

4. Method of Use (continued)	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information.</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number (as listed in the patent) 10	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify the use with specificity the use with reference to the proposed labeling for the drug product.	Use (Submit indication or method of use information as identified specifically in the approved labeling.) Treatment of mild-to-severe heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitor, and digitalis, to increase survival

4. Method of Use (continued)	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information.</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number (as listed in the patent) 11	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify the use with specificity the use with reference to the proposed labeling for the drug product.	Use (Submit indication or method of use information as identified specifically in the approved labeling.) Treatment of mild-to-severe heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitor, and digitalis, to increase survival

EXCLUSIVITY SUMMARY

NDA # 22-012

SUPPL # N/A

HFD # 110

Trade Name Coreg CR

Generic Name carvedilol phosphate

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

Approval Date, If Known October 20, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

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 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.

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES NO

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

3 Years

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

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES NO

IF THE ANSWER TO QUESTION 2 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 NO

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

NDA# 20-297

Coreg (carvedilolo) Tablets

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. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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 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 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:

N/A

(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

(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:

N/A

(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

If yes, explain:

N/A

- (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:

Study 367: A Randomized, Double-Blind, Multicenter Study Comparing the Effects of Administration of Modified Release Coreg or Placebo on Blood Pressure in Essential Hypertension Patients.

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

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

N/A

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

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

N/A

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"):

Study 367: A Randomized, Double-Blind, Multicenter Study Comparing the Effects of Administration of Modified Release Coreg or Placebo on Blood Pressure in Essential Hypertension Patients.

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 # 70,154 YES ! 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

If yes, explain:

N/A

Name of person completing form: Melissa Robb

Title: Regulatory Health Project Manager

Date:

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.

Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Melissa Robb
10/20/2006 03:56:58 PM

Norman Stockbridge
10/20/2006 04:06:06 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA #: 22-012 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: December 21, 2005 PDUFA Goal Date: October 21, 2006

HFD-110 Trade and generic names/dosage form: Coreg CR (carvedilol phosphate) Extended-Release Capsules

Applicant: SB Pharmco Puerto Rico Inc. d/b/a GlaxoSmithKline Therapeutic Class: Beta-Blocker

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next section.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 3

Indication #1: Essential hypertension

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Mild to Severe Heart Failure

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed
 NOTE: More than one may apply
 Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: Studies with Immediate-release formulation currently under review with the Division

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

Indication #3 : Reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of $\leq 40\%$

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: _____ Partial Waiver _____ Deferred _____ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 22-012
HFD-960/ Rosemary Addy or Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 6-23-2005)

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

/s/

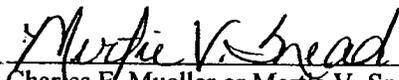
Melissa Robb

10/24/2006 09:30:37 AM

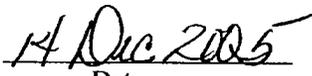
NDA 22-012 COREG (carvedilol phosphate) Controlled Release (CR) Capsules
for the treatment of hypertension and heart failure, and left ventricular dysfunction following
myocardial infarction

DEBARMENT CERTIFICATION

GlaxoSmithKline hereby certifies that it did not and will not use in any capacity the services of
any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection
with this application.



Charles E. Mueller or Mertie V. Snead
Director, North America Clinical Compliance
Worldwide Regulatory Compliance



Date

ACTION PACKAGE CHECKLIST

Application Information		
BLA # N/A NDA # 22-012	BLA STN# N/A NDA Supplement # N/A	If NDA, Efficacy Supplement Type N/A
Proprietary Name: Coreg CR Established Name: carvedilol phosphate Dosage Form: extended-release capsules		Applicant: SB Pharmco Puerto Rico d/b/a GlaxoSmithKline
RPM: Melissa Robb		Division: 110 Phone # 796-1138
NDAs: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. <input type="checkbox"/> If no listed drug, check here and explain: Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct. <input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date:
❖ User Fee Goal Date		October 21, 2006
❖ Action Goal Date (if different)		
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 3	
NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other: Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
Summary Reviews	
<p>❖ Summary Reviews (e.g., Office Director, Division Director) (<i>indicate date for each review</i>)</p>	<p>Division Director, 10/13/06 Medical Team Leader, 10/24/06</p>
<p>❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (<i>indicate date</i>)</p>	<p>N/A</p>
Labeling	
<p>❖ Package Insert</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>Included with Action Letter</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	<p>N/A</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>X</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	<p>X</p>
<p>❖ Patient Package Insert</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>N/A</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	<p>N/A</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>N/A</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	<p>N/A</p>
<p>❖ Medication Guide</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>N/A</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	<p>N/A</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>N/A</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	<p>N/A</p>
<p>❖ Labels (full color carton and immediate-container labels)</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	<p>N/A</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	<p>X</p>
<p>❖ Labeling reviews and minutes of any labeling meetings (<i>indicate dates of reviews and meetings</i>)</p>	<p><input checked="" type="checkbox"/> DMETS 6/2/06, 10/20/06 <input type="checkbox"/> DSRCs <input checked="" type="checkbox"/> DDMAC 8/9/06 <input type="checkbox"/> SEALD <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs</p>

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (indicate date of each review)	RPM Filing Review- 3/2/06 PM Overview; 10/24/06
❖ NDA and NDA supplement approvals only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	N/A N/A
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (Include certification.)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (if located elsewhere in package, state where located) Incoming submission documenting commitment 	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	X
❖ Internal memoranda, telecons, email, etc.	N/A
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Pre-Approval Safety Conference (indicate date; approvals only) Pre-NDA/BLA meeting (indicate date) EOP2 meeting (indicate date) Other (e.g., EOP2a, CMC pilot programs) 	N/A <input type="checkbox"/> No mtg 6/15/05; 7/21/05 <input type="checkbox"/> No mtg 8/25/04; 9/22/04 4/30/03; 8/6/03; 11/25/03; 5/24/04; 3/1/05
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available 	N/A N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Product Quality Information	
❖ CMC/Product review(s) (indicate date for each review)	1/30/06; 8/14/06; 9/25/06; 10/16/06
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population) <input type="checkbox"/> Review & FONSI (indicate date of review) <input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review) 	8/14/06
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (indicate date of each review)	<input checked="" type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> NDAs: Facilities inspections (include EER printout) 	Date completed: 10/13/06 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	9/27/06
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	8/30/06
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	8/30/06
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	9/5/06
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	8/30/06
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
• Clinical Studies	8/8/06
• Bioequivalence Studies	10/19/06
• Clin Pharm Studies	N/A
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/16/06
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/15/06; 10/12/06

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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

/s/

Melissa Robb

10/24/2006 09:41:22 AM

Project Manager Overview
NDA 22-012
Coreg CR (carvedilol phosphate) Extended-release Capsules

Overview:

NDA 20-297, Coreg (carvedilol), is currently approved as an immediate release formulation for the treatment of essential hypertension, mild to severe congestive heart failure, and to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of <40%. For all three indications, carvedilol is to be taken twice daily.

The sponsor submitted NDA 22-012, Coreg CR (carvedilol phosphate) Extended-release Capsules, on December 21, 2005. This formulation will require once daily dosing. The sponsor is seeking approval for the same indications for which the immediate release formulation is approved.

Division Director's Memo

Dr. Norman Stockbridge; October 13, 2006

In his memo, Dr. Stockbridge stated that the pharmacokinetic properties of the sustained-release carvedilol were similar to those of immediate-release carvedilol after suitable adjustments were made in total dose with respect to AUC and C_{max}. The ABPM study demonstrated effects on systolic and diastolic pressure throughout the interdosing interval. Beta-blockade fell within the 80-125% confidence limits of the immediate-release formulation for both AUC and maximum fact. He also noted that the intra-subject variability in pharmacokinetics has been carefully assesses and the new formulation appears to perform satisfactorily.

Medical Review

Dr. Abraham Karkowsky, October 24, 2006

In his review, Dr. Karkowsky addressed the issues raised by the DSI review done by Dr. Jagan Mohan R. Parepally. Dr. Karkowsky concluded that although there were substantial deviations from good clinical practice at the site of _____, he believes the data can still be relied upon as sufficiently accurate to support the study. Dr. Stockbridge concurred.

Medical Review

Dr. Akinwole Williams; August 30, 2006

In his review, Dr. Williams recommended the approval of this NDA for the indications sought. However, Dr. Williams included some reservations about the statistical analyses of the secondary efficacy variables. Dr. Williams noted the sponsor's proposed risk management plan consisting of the use of the approved package insert, routine

pharmacovigilance activities, and surveillance of adverse events in the Phase 3B program.

Financial Disclosure: On pages 83-84 of his review, Dr. Williams states that the certificate of financial disclosure was submitted and that financial interest information from all the clinical investigators participating in studies was acceptable.

120-Day Safety Update Review

Dr. Akinwale Williams; September 5, 2006

Dr. Williams stated that this update added approximately 24% to the total number of patients exposed to Coreg CR since the time of the NDA filing. Although this data is blinded, Dr. Williams stated that there is no evidence to suggest a change in the safety profile of Coreg CR.

Statistical Review

Dr. Steven Bai; August 14, 2006

In his review, Dr. Bai concluded that the data supports that Coreg CR, alone or in combination with other therapies, at doses of 20, 40, and 80 mg once daily causes a clinically and statistically significant reduction in blood pressure compared to placebo.

Pharmacology Review

Dr. Albert DeFelice; September 27, 2006

Dr. DeFelice reviewed two potential safety issues with the extended-release formulation component, which is associated with "hypersensitivity" clinically with the . In addition, promotes the formation of a degradant, also a potentially genotoxic impurity.

Dr. DeFelice recommended no further testing by the sponsor for either issue.

Chemistry Reviews

Dr. Eugenia Nashed; October 16, 2006

In her review, Dr. Nashed stated that the application is recommended for approval from a Chemistry, Manufacturing, and Controls (CMC) perspective. An acceptable GMP status is available from the Office of Compliance as of October 13, 2006. Her review also included wording to be included in the action letter. Revised agreed-upon drug substance specifications were included.

Dr. Eugenia Nashed; September 25, 2006

In her review, Dr. Nashed stated that from a CMC perspective, the application is recommended for approval, provided that an acceptable GMP status is available for the

drug product manufacturing facility at Flamel Technologies in Pessac, France /

EER: Pending (see above)

Dr. Eugenia Nashed; August 11, 2006

In her review, Dr. Nashed stated that the application is approvable at this time. Comments have been forwarded to the sponsor in Information Request letters dated August 2 and 11, 2006.

EA: Categorical Exclusion Acceptable

Dr. Kasturi Srinivasachar; January 30, 2006

Dr. Srinivasachar stated that this NDA is filable and should be reviewed by a single reviewer.

Clinical Pharmacology Reviews

Dr. Christine Garnett; October 12, 2006

In her review, Dr. Garnett listed the recommended dissolution method and specifications:

The dissolution method is USP Apparatus II, paddle speed of 100 rpm, in 0.1N HCL dissolution medium at 37°C. The vessel volume is 900 ml. The four time point specification expressed as % label claim is not more than — at 1-h, not less than — and not more than — at 8-h, not less than — and not more than — at 18-h, and not less than — at 24-h.

She also stated that a biowaiver for the level II site change can be granted for all capsule strengths.

Dr. Christine Garnett; September 15, 2006

In her review, Dr. Garnett stated that the NDA is considered acceptable from a clinical pharmacology perspective. Some recommendations on dissolution and labeling were included in her review.

Division of Scientific Investigations Reviews

Clinical Inspection

Dan-My Chu; July 31, 2006

The Division of Scientific Investigations stated in general the sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. There was a finding at Dr. Chrysant's site where the primary efficacy

endpoint was reported as a whole number in the — ABPM reports and the data listing used decimal points. It was recommended that the Division evaluate this to determine whether or not this impacts the statistical significance of the data in support of this NDA.

Bioequivalence Studies

Jagan Mohan R. Parepally, Ph.D.; October 19, 2006

The Division of Scientific Investigations investigated 2 of the 32 sites for Study 369, an open label, non-randomized comparison of pharmacokinetic profiles of carvedilol modified release and immediate release on repeat dosing in chronic congestive heart failure patients and asymptomatic survivors of an acute myocardial infarction and left ventricular dysfunction. They concluded that one site failed to conduct the study according to protocol and recommended that the data be excluded from consideration.

DMETS Review

In a review dated October 20, 2006, DMETS stated that they have no objection to the use of the proprietary name, Coreg CR. They also provided comments for the container and carton labels resubmitted by the sponsor. It was also noted that DDMAC found the name Coreg CR acceptable from a promotional perspective.

In a review dated June 2, 2006, DMETS stated that the addition of "CR" to Coreg does not pose additional concerns with the introduction of Coreg CR. DMETS also identified some labeling comments that were conveyed to the sponsor in a letter dated July 6, 2006. It was also noted that DDMAC found the name Coreg CR acceptable from a promotional perspective.

DDMAC Review

In a review dated August 9, 2006, DDMAC provided some comments on the proposed package insert.

Action:

An approval on draft letter will be drafted.

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/s/

Melissa Robb
10/24/2006 09:23:17 AM
CSO

MEMORANDUM

Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
WO 22, Mailstop 4447, HFD-420
Center for Drug Evaluation and Research

To: Norman Stockbridge, MD
Director, Division of Medical Cardiovascular and Renal Products
HFD-110

Through: Linda Kim-Jung, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Kristina C. Arnwine, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: September 25, 2006

OSE Review # 2006-308, Coreg CR (Carvedilol Extended-release Capsules) 10 mg, 20 mg, 40 mg, and 80 mg;
NDA 22-012

This memorandum is in response to a September 20, 2006 request from your Division for a re-review of the proprietary name Coreg CR. Container labels were also submitted for review and comment.

The proposed proprietary name was found acceptable by DMETS in OSE Review 04-236 (dated February 11, 2005) and in OSE Review 06-0033 (dated June 2, 2006). Since the initial review of Coreg CR, DMETS has identified the names Crestor, Koate, Corfen DM, and Corphed as names that have the potential to look and/or sound similar to Coreg CR. Koate, Corfen DM, and Corphed will not be reviewed further due to a lack of convincing orthographic and/or phonetic similarity in addition to differentiating product characteristics such as product strength, dosage form, usual dose, and/or dosing frequency.

A. Look-Alike Concerns

Crestor was identified as name that looks similar to Coreg CR. Crestor is an HMG-CoA reductase inhibitor indicated for the reduction of cholesterol.

Coreg CR and Crestor both begin with the letter 'C' and have the letters 're' presented in the middle portion of each name which are the principal contributors to the look-alike characteristics of each name. However, the letter 'o' in Coreg CR causes the beginning portions of each name to differ. Additionally, the downstroke of the letter 'g' at the end of Coreg CR and the upstroke of the letter 't' in Crestor cause the endings of each name to differ orthographically as well. Furthermore, upon approval of this product, the availability of more than one dosage form of Coreg will necessitate prescribers to specify which dosage form they desire to prescribe, which should help to further distinguish the two names from each other.

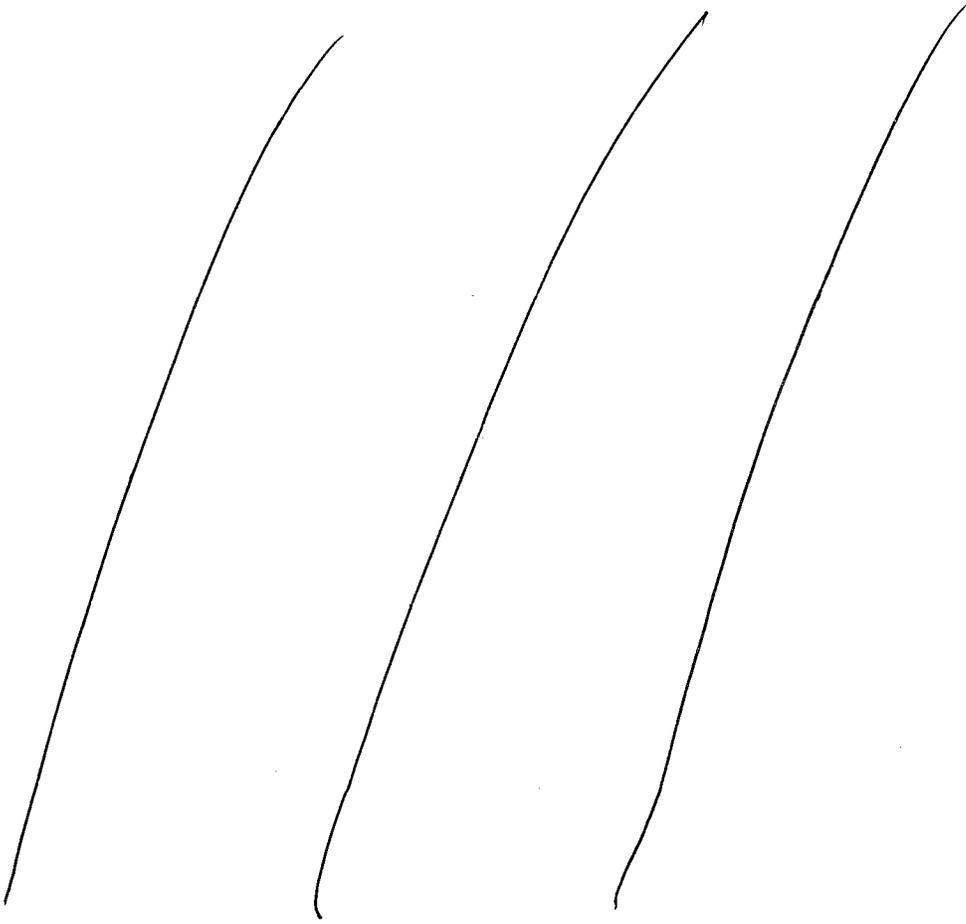
Coreg CR
Crestor

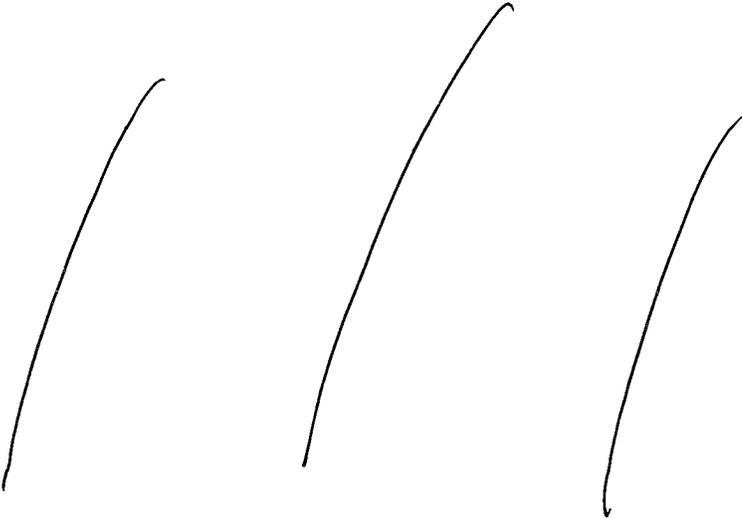
With regard to product characteristics, Coreg CR and Crestor are both solid oral dosage form (capsules vs. tablets) that are taken once daily. Additionally, Coreg CR and Crestor have overlapping product strengths (**10 mg, 20 mg, 40 mg**, and 80 mg vs. 5 mg, **10 mg, 20 mg, and 40 mg**). The usual doses can overlap as well (10 mg to 80 mg vs. 5 mg to 40 mg). Despite the overlapping product characteristics, the letter 'o' in Coreg CR in addition the differing endings of each name and the differing dosage forms help to distinguish Coreg CR from Crestor.

B. Safety Concerns With Modifier 'CR'

In OSE Review 06-0033 DMETS recommended that the Division contact the CDER Labeling and Nomenclature Committee with regard to the established name, which at the time was "Carvedilol Controlled-release Capsules". DMETS notes that the established name has been revised to "Carvedilol Extended-release Capsules" which is in accord with USP recognized dosage forms. There are currently six prescription products listed in the Orange Book that use the "CR" modifier (Paxil CR, Ambien CR, Dynacirc CR, Afeditab CR, Sinemet CR, and Norpace CR). Four of these products can be dosed once daily (Paxil CR, Ambien CR, Dynacirc CR, and Afeditab CR), while the remaining two products (Sinemet CR, and Norpace CR) can be dosed more than once per day. Thus to avoid ambiguity over the dosing interval, _____

C. Label and Labeling Safety Issues





In summary, DMETS has no objections to the use of the proprietary name, Coreg CR. We recommend implementation of the above labeling comments in order to minimize medication errors with the use of this product. Additionally, the Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the name Coreg CR acceptable from a promotional perspective. We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Diane Smith at 301-796-0538.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Kristina Arnwine
10/20/2006 04:04:36 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
10/20/2006 04:06:52 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/20/2006 04:14:53 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

DATE: September 29, 2006

TO: Norman Stockbridge, M.D.
Director
Division of Cardio-Renal Products

FROM: Jagan Mohan R. Parepally, Ph.D.
Staff Fellow
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. CV 10/11/06
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 22-012,
Coreg CR (Carvedilol Phosphate) Capsules,
Sponsored by SB Pharmco Puerto Rico, Inc.

At the request of the Division of Cardiac and Renal Products (DCRP), the Division of Scientific Investigations (DSI) conducted an audit of the clinical portion of following bioequivalence study:

Study SK&F-105517/369: An open label, non-randomized comparison of pharmacokinetic profiles of carvedilol (SK&F-105517) modified release (MR) and immediate release (IR) on repeat dosing in chronic congestive heart failure (CHF) patients and asymptomatic survivors of an acute myocardial infarction (MI) and left ventricular dysfunction (LVD).

This was a multicenter study conducted at 32 clinical sites. Three clinical sites were selected for inspection and one of the inspections was cancelled later at the request of the review division. Following the inspection of clinical investigators _____

(May 2-15, 2006) and _____
June 12-16, 2006), Form FDA-483 was issued at each site (Attachment 1). The objectionable items and our evaluation are provided below:

Dr. _____

1. The study was not conducted in accordance with the investigational plan (See attached Form FDA-483 for more details).
 - a. Five (5) out of 17 subjects who received at least one dose of study drug did not meet eligibility criteria in that 3 subjects had left ventricular ejection fraction (LVEF) greater than the protocol allowed limit, one subject received protocol prohibited medication and another subject's creatinine level was greater than that allowed by the protocol.

The above observation along with observations 1b, 1d, 1e, 1g, and 1i below are protocol deviations related to safety of the human subjects enrolled in the study. Specifically, the protocol criteria for LVEF and creatinine level were not met at screening for some patients. The impact of elevated LVEF levels and creatinine and the prohibited medication on the pharmacokinetics of Coreg CR cannot be assessed. Dr. _____ failed to protect the well-being of the subjects and conduct the study according to the investigational plan. In response to the Form FDA-483, Dr. _____ agreed to avoid such mistakes in future studies.

- b. There is no documentation of the completion of physical exams, as required by the protocol, for the study visits 1, 3, and 4 for 20 out of 20 subjects who completed at least study visit 1.
- c. Pharmacokinetic day meal standardization was not followed according to the protocol for visits 3 and 4. There is no documentation for all the subjects who received study drug in the following areas: an eight hour fast prior to PK sampling day, calorie (<25% from fat) content of breakfast or dinner, consumption of breakfast and dinner within 30 minutes, administration of study drug within 5 min of meal consumption, lunch after 4 hours PK sample and abstention from water for 2 hours after dosing and from soft drinks and fruit juice for 4 hours after dosing.

It is not assured that the protocol was followed in these matters because there is no documentation.

- d. Ten (10) out of 17 subjects who received at least one dose of study drug did not have a chest X-ray done prior to receiving study drug. The protocol requires that chest x-rays be completed during visit 1 or within 6 months prior to visit 1.
- e. It cannot be determined if two (2) subjects met the protocol eligibility criteria as blood chemistries were not evaluated prior to administration of study drug due to hemolysis of the specimens and blood chemistries were not repeated prior to study drug administration. The chemistries were not conducted for subjects 001111 and 001117.
- f. The site did not comply with the IRB's SAE reporting requirement, as required by the protocol in that they did not report a SAE (intracranial hemorrhage resulting in death) that occurred in a study subject receiving study drug.

Observation 1f is related to safety of the subjects and do not affect the study outcomes.

- g. There is no documentation of routine urinalysis results, performed at the site via dipstick as required by the protocol for study visit 1, for 20 out of 20 subjects.
- h. There is no documentation of sample preparation and storage, including sample chilling and centrifuging, plasma transfer, and storage at -20°C for all the subject samples in both PK sampling periods.

According to the stability data from the validation report, carvedilol is stable in plasma at room temperature for at least 4 hours. The stability of carvedilol in blood samples is not evaluated. This observation may affect the integrity of study samples. The site needs to correct this objectionable observation.

- i. Site failed to document LVEF values for 2 subjects within one year according to the protocol.

2. The Investigator did not retain a reserve sample of the test article and reference standard used in this study.

The site failed to retain reserve samples as required by the bioequivalence regulations [21 CFR 320.38 and 320.63]. The identity of the product dosed to subjects cannot be confirmed through the reserve samples.

3. Investigational drug disposition records are not adequate with respect to quantity and use by subjects in that there is no documentation for 2 subjects dosed with Coreg MR and 8 subjects with Coreg IR.

The drug product accountability records are incomplete.

4. Failure to prepare and maintain adequate case histories with respect to observations and data pertinent to the investigation in that there were no subject identifiers for ECGs for 2 subjects and ECG was not recorded for a subject 001113.

The ECGs cannot be attributed positively to subjects 001112 and 001114.

Dr.

1. Reserve samples of the test article, Coreg MR, and the reference standard, Coreg IR used in the conduct of this study were not retained at the study site and were not available for sampling during inspection.

The site failed to retain reserve samples as required by the bioequivalence regulations [21 CFR 320.38 and 320.63]. The identity of the product dosed to subjects cannot be confirmed through the reserve samples.

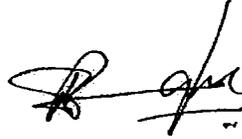
Conclusion:

Dr. — site failed to conduct Study SK&F-105517/369 according to the protocol. Due to extensive non-compliance with study protocol, DSI recommends that the data obtained from all the subjects at Dr. — site be excluded from consideration. The OCP reviewer should evaluate the impact of excluding the subject data obtained from this site on the overall study outcome. In addition, both study sites

Page 5 of 5 - NDA 22-012, Coreg CR (carvedilol phosphate)
Capsules

failed to retain reserve samples as required by the
bioequivalence regulations [21 CFR 320.38 and 320.63].

After you have reviewed this transmittal memo, please
append it to the original NDA submission.



Jagan Mohan R. Parepally, Ph.D.

Final Classifications:

_____ - OAI

_____ - VAI

CC:

HFD-45/RF

HFD-48/Parepally/Himaya/CF

DCRP/Robb/Garnett (WO22, RM4154, NDA 22-012)

HFR-CE1515/Tammariello/McClure

HFR-CE250/Salisbury/Shapley

HFR-CE 150/Rashti/Joyce-Pittman

Draft: JP 09/26/06

Edit: MKY 09/29/06

Edit: MFS 09/29/06

DSI: 5692; O:\BE\EIRCOVER\22012 Coreg CR.doc

FACTS: 724920

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/s/

Jagan Parepally
10/19/2006 11:46:32 AM
PHARMACOLOGIST

MEMORANDUM OF TELECON

DATE: September 25, 2006

APPLICATION NUMBER: NDA 22-012

BETWEEN: Name: Scott Ziegenfuss
Phone: 610-917-6421
Representing: GlaxoSmithKline

AND Name: Scott N. Goldie, Ph.D., ONDQA/DPMAI

SUBJECT: Post Approval Stability Commitment

GSK has submitted NDA 22-012 for COREG CR. CMC Reviewer Jean Nashed requested confirmation that the standard post approval stability commitment, (i.e. the first 3 commercial batches of each strength and each package configuration would be placed on stability, in accordance with published guidances. This did not appear in the September 22, 2006 submission to update m3.2.P.8.2, post approval stability protocol and stability commitment. Jean asked that I contact the sponsor (Scott Ziegenfuss) and request confirmation.

Scott Ziegenfuss confirmed that three batches of all capsule strengths would be placed on stability, and that the module would be updated to reflect this commitment. A desk copy was faxed to SNG (attached). Scott Ziegenfuss further cited the preNDA CMC meeting minutes dated July 7, 2005, which indicate that 1 batch of all package configurations would be included in the post approval stability protocol, but not three of each package type. Jean confirmed this in the meeting minutes and found GSK's proposal acceptable.

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Eugenia Nashed, Ph.D.
Review Chemist
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Scott Goldie
9/27/2006 09:24:25 AM
PROJECT MANAGER FOR QUALITY

Eugenia Nashed
9/27/2006 10:16:49 AM
CHEMIST

Minutes of a Teleconference

Application Number: 22-012

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

Drug: Coreg CR (carvedilol phosphate) Extended-release Capsules

Teleconference Date: September 20, 2006

List of Attendees:

Division of Cardiovascular and Renal Products

Patrick Marroum, Ph.D.	Team Leader Division of Clinical Pharmacology I
Christine Garnett, Pharm.D.	Pharmacometrics Reviewer Office of Clinical Pharmacology
Eugenia Nashed, Ph.D.	Chemist Office of New Drug Quality Assessment
Melissa Robb	Regulatory Health Project Manager Division of Cardiovascular and Renal Products Division of Cardiovascular and Renal Products

GlaxoSmithKline

Patrick Crowley	Pharmaceutical Development
Choon Oh	Pharmaceutical Development
Albert Kearney	Pharmaceutical Development
Jim Zisek	CMC Regulatory Affairs
Norma Collinsworth	CMC Regulatory Affairs
Ron Mueller	Pharmaceutical Development
Alireza Kord	CD

BACKGROUND

NDA 20-297, Coreg (carvedilol), is currently approved as an immediate release formulation for the treatment of essential hypertension, mild to severe congestive heart failure, and to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of <40%. For all three indications, carvedilol is to be taken twice daily. The sponsor submitted NDA 22-012 for Coreg CR (carvedilol phosphate) Extended-release Capsules on December 21, 2005. This formulation will require once daily dosing. The sponsor is seeking approval for the same indications for which the immediate release formulation is approved. A teleconference was held on September 15, 2006 to discuss the Agency's concerns about the sponsor's proposed dissolution specifications. This teleconference was scheduled to follow-up on the dissolution specifications and discuss other outstanding Chemistry, Manufacturing, and Controls (CMC) issues.

DISCUSSION

The Agency began by stating that they have reviewed the data submitted to support the paddle rotation speed of 100 rpm and agree that it is acceptable.

The sponsor stated that at the last teleconference they agreed to an additional timepoint at 18 hours. They are proposing a limit of not less than _____ at the 18 hour timepoint. The Agency stated that _____

_____. The sponsor proposed a range of _____. The Agency stated that the sponsor would need data to support that wide of a range. The sponsor suggested a range of _____. The Agency inquired if any batches have failed at _____. The sponsor stated that they are concerned with _____, because 2 of the primary stability batches have means of around _____ at 12 months and 18 months. The Agency agreed that _____ would be acceptable provided that the sponsor committed to reviewing the specifications after production of the _____ commercial batches and tighten the specifications, if appropriate. The sponsor agreed. The Agency requested that this data be submitted in the annual report for review. The final agreed-on specifications for drug product dissolution are as follow:

1 hour: NLT _____ Label Claim
8 hours: _____ Label Claim
18 hours: _____ Label Claim
24 hours: NLT _____ Label Claim

The Agency stated that the sponsor's proposal regarding tightening residual solvents specifications, included in their e-mail to Melissa Robb on September 20, 2006 (attached), is acceptable. The Agency requested that these specifications also be reviewed and tightened, as warranted, based on the data from the _____ commercial batches produced. The Agency requested review for all residual solvent levels (drug substance and microparticles) but was especially concerned with the _____ levels. The sponsor agreed.

The Agency stated that the sponsor's proposal regarding tightening specifications for particle size distribution in the drug substance, included in their e-mail to Melissa Robb on September 20, 2006 (attached), is acceptable. However, the Agency noted that the limits proposed do not represent the data submitted. In order to allow the sponsor the greatest flexibility to refine their drug substance, the Agency stated that they would like the sponsor to review the data from the drug substance used in the _____ commercial batches of drug product and tighten these specifications to reflect the data. The Agency noted concern with the _____ limit. The sponsor agreed.

The Agency stated that the sponsor's proposal _____ is acceptable. The Agency requested that appropriate SOPs be updated to clarify _____ . The sponsor agreed.

The Agency stated that the sponsor's plan to address the use of _____ microparticles and manufacturing changes for the full scale drug product, included in their e-mail to Melissa Robb on September 20, 2006 (attached), is acceptable. The Agency requested that when this data is submitted a side-by-side comparison of dissolution profiles be included comparing the _____ microparticle batches and drug product manufactured from _____ microparticles. The sponsor stated that they would include a description of how representative the batches are with their submission. The sponsor confirmed that they plan to use _____ packaging for the commercial drug product.

It was agreed by the Agency and the sponsor that the data on the _____ commercial batches would be included in the annual report. If this data collection is not complete at the time of the first annual report, a status update will be included. When this data are submitted in the annual

report, the sponsor will clearly note in the cover letter the inclusion of the agreed-upon data for review.

The sponsor stated that they would submit official responses to all CMC Discipline Review letters, either via the Gateway or the Central Document Room. The submitted responses will be identical to the responses submitted earlier by e-mail and will also reflect all updates and agreements reached during teleconferences on September 15, and 20, 2006.

Recorder: *{See appended electronic signature page}*

Chair Concurrence: *{See appended electronic signature page}*

Drafted: 9/20/06 Finaled: 9/27/06

RD:

Marroum	9/22/06
Garnett	9/20/06
Nashed	9/20/06

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/s/

Melissa Robb
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Patrick Marroum
9/27/2006 04:39:10 PM

Minutes of a Teleconference

Application Number: 22-012

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

Drug: Coreg (carvedilol phosphate) Extended-release Capsules

Teleconference Date: September, 15, 2006

List of Attendees:

Division of Cardiovascular and Renal Products

Patrick Marroum, Ph.D.	Team Leader Division of Clinical Pharmacology I
Christine Garnett, Pharm.D.	Pharmacometrics Reviewer Office of Clinical Pharmacology
Eugenia Nashed, Ph.D.	Chemist Office of New Drug Quality Assessment
Melissa Robb	Regulatory Health Project Manager Division of Cardiovascular and Renal Products

GlaxoSmithKline

Patrick Crowley	Pharmaceutical Development
Choon Oh	Pharmaceutical Development
Albert Kearney	Pharmaceutical Development
Lingling Rogers	Pharmaceutical Development
Alex Henderson	Global Manufacturing Supply (Crawley, UK)
David Lines	Global Manufacturing Supply (Crawley, UK)
Jim Zisek	CMC Regulatory Affairs
Scott Ziegenfuss	CMC Regulatory Affairs

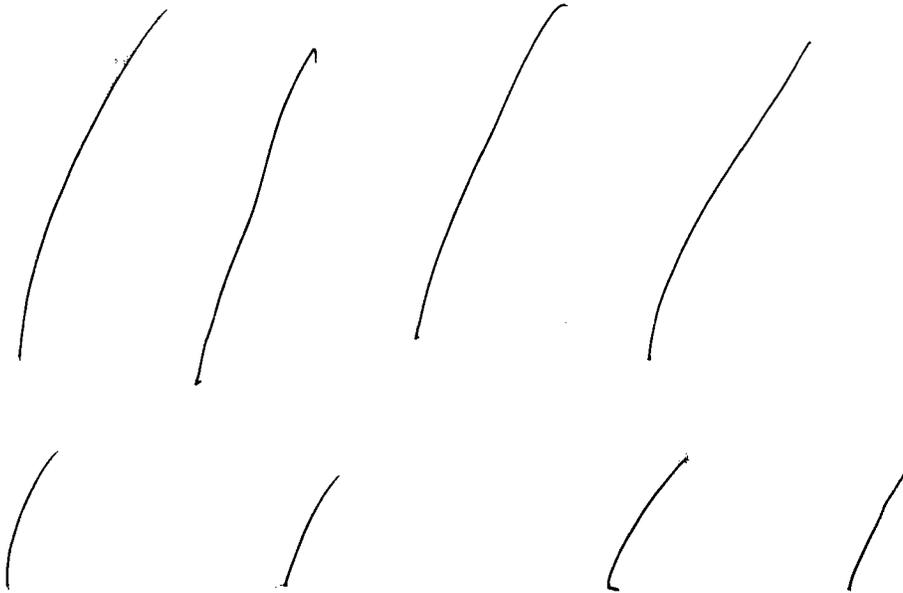
BACKGROUND

NDA 20-297, Coreg (carvedilol) Tablets, is currently approved as an immediate release formulation for the treatment of essential hypertension, mild to severe congestive heart failure, and to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of <40%. For all three indications, carvedilol is to be taken twice daily. The sponsor submitted NDA 22-012 for Coreg (carvedilol phosphate) Extended-release Capsules on December 21, 2005. This formulation will require once daily dosing. The sponsor is seeking approval for the same indications for which the immediate release formulation is approved. This teleconference was scheduled to discuss the Agency's concerns about the sponsor's proposed dissolution specifications.

DISCUSSION

The Agency began by inquiring why the sponsor is proposing to use a paddle rotation speed of 100 rpm, rather than 150 rpm. The sponsor believes that, as was depicted in Table 3 of the e-mail sent to the Division on September 14, 2006 (attached), the paddle rotation speed of 100 rpm results in appropriate discrimination. The sponsor stated that the higher paddle rotation speed is

appropriate with a controlled release formulation because it will



The sponsor noted that all data collected to date used the 100 rpm paddle speed.

The next issue discussed was tightening the specification at 8 hours. The sponsor stated that this request was made by not only the clinical pharmacologist, but also the chemist. The sponsor has revised their proposed lower limit from — the Agency had proposed — The sponsor expressed concern about establishing shelf-life.

The Agency inquired if the batches presented in Table 1 of the e-mail sent to the Division on September 14, 2006 (attached), are representative of the clinical and to-be-marketed batches. The sponsor stated that most individual values were — after scale-up some were as high as

— The sponsor confirmed that the commercial batches were not tested clinically and the changes in the batches were related to scale-up and a new manufacturing building. The Agency was also concerned how a change in paddle speed (from 100 rpm

— would affect these findings.

The sponsor proposed an interim range of — with a post-marketing commitment to tighten that range based on the results of the — commercial batches. The Agency stated that the issue of paddle speed would first need to be resolved prior to commenting on this proposal.

The last issue discussed was the final specification timepoint. The Agency stated that guidances recommend that final specification timepoint occur when there is 80% dissolution. The sponsor is proposing the final timepoint at 24 hours, which would result in testing at 1, 8, and 24 hours. The Agency expressed concern that this would allow in drug product batches with different profiles. The Agency stated that this proposal would be acceptable if the sponsor agreed to test the batches at another timepoint between 8 and 24 hours. The sponsor stated that they will do testing at either 12 or 18 hours. The Agency stated acceptable ranges would need to be agreed

upon. The Agency believes that the more timepoints evaluated the better to ensure a quality product. The sponsor stated that they plan to collect the additional data at 18 hours.

The Agency stated that they will review _____ to determine if the 100 rpm paddle speed is sufficiently discriminating. If this is the case, the Agency stated that it is likely that the proposal for the interim range of _____ at 8 hours will be acceptable.

The Agency noted that four of the primary stability batches are not meeting specifications, and suggested the sponsor submit any rationale they are aware of to support the differences between the batches meeting the specifications and those that are not.

The Agency concluded by stating that there are some CMC issues that will need additional follow-up discussions in the next few weeks. These issues include residual solvents, particle size distribution for the drug substance, the _____ and manufacturing changes as linked to the drug product performance.

Recorder: *{See appended electronic signature page}*

Chair Concurrence: *{See appended electronic signature page}*

Drafted: 9/18/06 Finalized: 9/20/06

RD:

Marroum	9/20/06
Garnett	9/18/06
Nashed	9/18/06

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Melissa Robb
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Patrick Marroum
9/20/2006 02:50:10 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-012

INFORMATION REQUEST LETTER

SB Pharmco Puerto Rico Inc. d/b/a GlaxoSmithKline
Attention: Scott Ziegenfuss, Assistant Director, US Regulatory Affairs
One Franklin Plaza
200 N. 16th Street
Philadelphia, PA 19102

Dear Mr. Ziegenfuss:

Please refer to your December 21, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coreg CR (carvedilol phosphate) extended-release capsules, 10, 20, 40, and 80 mg.

We also refer to your submissions dated June 30, 2006, and July 10, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA:

1. Please include the following additional information in the revised specifications sheet for drug substance which was requested in comment #3 of our Information Request Letter dated August 2, 2006:

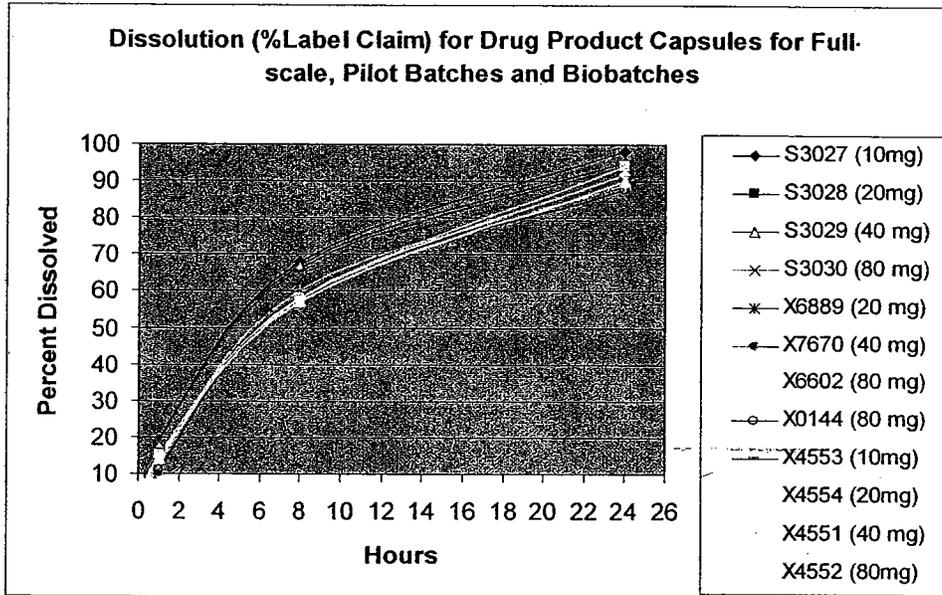
a.

/ /

- a.
- b. Revise the acceptance criteria for particle size distribution to provide, at the minimum, _____

/ / /

2. Explain the noticeably different dissolution profiles for the drug product batches prepared from the full-scale microparticle batches manufactured in the new building (upper red lines) and the drug product prepared from the full-scale batches manufactured in the pilot building (lower blue lines), which seems to be comparable to bio-batches (yellow and light green lines). Refer to the plot below. We note that the most pronounced difference occurs at the 8 hours data point and recommend tightening the proposed acceptance criteria for this dissolution point, to reflect the data for the to-be-marketed drug product.



3. The following are preliminary comments on the proposed container and carton labels. Additional comments on the proposed labeling will be provided during later stages of the review:

[Handwritten scribbles]

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

cc: SB Pharmco Puerto Rico Inc. d/b/a GlaxoSmithKline
Attention: Scott Ziegenfuss, Assistant Director, US Regulatory Affairs
1250 S. Collegeville Road
PO Box 5089
Collegeville, PA 19426-0989
Phone: (610) 917-4704
Fax: (610) 914-6421

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/s/

Ramesh Sood
8/11/2006 10:25:43 AM



NDA 22-012

INFORMATION REQUEST LETTER

SB Pharmco Puerto Rico Inc. d/b/a GlaxoSmithKline
Attention: Catherine K. Clark
One Franklin Plaza
200 N. 16th Street
Philadelphia, PA 19102

Dear Ms. Clark:

Please refer to your December 21, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coreg (carvedilol phosphate) Controlled Release Capsules, 10, 20, 40, and 80 mg.

We also refer to your submission dated June 30, 2006, which is currently under review. Comments regarding this submission are not included in this information request letter.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA:

The following comments pertain to drug substance manufacturing and controls.

1. Submit a specification sheet for acceptance testing of the incoming _____ Include a full list of test attributes, individual method numbers and corresponding acceptance criteria.
2. Revise the "Detailed description of the manufacturing process" (m3.2.S.2.2) by implementing the following changes:

/ / / / /

D

6 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

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/s/

Ramesh Sood
8/2/2006 07:19:33 AM

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: July 27, 2006

TO: Melissa Robb, Regulatory Project Manager
Akinwole Williams, MD, Medical Reviewer
Division of Cardiovascular and Renal Products

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Dan-My T. Chu, Ph.D.
Regulatory Review Officer
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-012

NME: No

APPLICANT: GlaxoSmithKline

DRUG: Coreg (carvedilol phosphate) controlled release (20, 40, or 80 mg capsules)

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of essential hypertension

CONSULTATION REQUEST DATE: March 10, 2006

DIVISION ACTION GOAL DATE: October 21, 2006

PDUFA DATE: October 21, 2006

I. BACKGROUND:

GlaxoSmithKline submitted a New Drug Application for Coreg (carvedilol phosphate) controlled release (CR) capsules for the treatment of essential hypertension, mild to severe chronic heart failure, and to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of myocardial infarction and have a left ventricular ejection fraction of less than/equal to 40% (with or without symptomatic heart failure). This is the same indication to which the twice daily (BID) immediate release formulation has been approved under NDA 20-297. The controlled release formulation allows once daily dosing of the drug, thus potentially improving patient compliance in taking the drug.

In support of the use of Coreg CR capsules in essential hypertension patients, chronic congestive heart failure patients and in myocardial infarction survivors with left ventricular dysfunction, the sponsor conducted two large multicenter studies (SK&F-105517/367 & SK&F-105517/369).

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State*	Protocol #	Insp. Date	EIR Received Date	Final Classification
7783 Deanna Cheung	Long Beach, CA	SK&F 105517/ 367	4/19-26/06	6/15/06	NAI
7791 Steven Chrysant	Oklahoma City, OK	SK&F 105517/ 367	5/23/06-6/5/06	6/30/06	VAI
7828 Larry Gilderman	Pembroke Pines, FL	SK&F 105517/ 367	5/4-10/06	5/30/06	NAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Protocol # SK&F 105517/367: This study examined the use Coreg CR capsules in the long-term management of essential hypertension. The primary objective of the study was to compare the effects on diastolic blood pressure (DBP) of three different doses of Coreg CR capsules to placebo in essential hypertension patients, as measured by changes from baseline in mean 24 hr DBP. The primary efficacy endpoint is the change from baseline DBP as measured by 24 hr ambulatory blood pressure monitoring (ABPM) device to the end of the up-titration treatment (6 weeks) or to early withdrawal. To measure the primary efficacy endpoint, the subject will wear the standard electronic ambulatory monitoring equipment for 24 hours of ambulatory activity. Data collected by the ABPM devices will include mean DBP, SBP and heart rate at various intervals.

This was a double-blind, randomized, placebo-controlled, parallel group, multi-center study comparing three doses of Coreg CR capsule with placebo in subjects with essential hypertension [sitting DBP of ≥ 90 and ≤ 109 mmHg]. The study was conducted in 5 phases: (1) In the screening phase, subjects will initially be screened over a 2-5 day period for eligibility after written informed consent has been obtained; (2) Once eligibility has been confirmed, subjects will enter a 2-4 week placebo run-in/washout phase where subjects currently taking beta blockers or clonidine are tapered off their medication during this phase. After the final dose of placebo, the ABPM device will be placed on subjects and the 12 hr day-time ABPM will be measured. Subjects will continue to wear the device for a full 24 hrs. The 12 hr daytime ABPM will establish entry level DBP and determine eligibility for entrance into the baseline/randomization phase; (3) At the randomization visit, the ABPM device will be removed and the 24 hr ABPM data checked to determine if the appropriate number of readings has been obtained. Subjects who satisfy all screening and inclusion criteria for entry will be randomized 1:1:1 to one of three doses of once-daily Coreg CR (20 mg, 40 mg or 80 mg) or placebo; (4) At the double-blind up-titration phase, subjects assigned to one of the three Coreg CR arms will start dosing at 20mg (once daily). At 2-week intervals, subjects will undergo blinded up-titration to their assigned randomized dose or the highest tolerated dose if the randomized target cannot be reached: 40mg Coreg CR, 80mg Coreg CR. Subjects randomized to placebo will receive placebo for six weeks. When the last dose of drug is given, the ABPM device will be placed on the subject for 24 hrs. (5) At the end of 24 hrs, the ABPM is removed and the data checked to determine if the appropriate number of readings has been obtained. Subjects will then enter the 2 week down-titration phase.

The sites chosen for inspection were made by the review division. These sites had the highest number of enrollments compared to other sites; hence there are concerns as to whether or not all subjects met the eligibility criteria.

Inspected:

1. Deanna Cheung, MD
2865 Atlantic Ave Ste 227
Memorial Research Medical Clinic
Long Beach, CA 90806
 - a. At this site, 29 subjects were screened; 17 subjects were randomized, 1 subject withdrew or terminated early, and 16 subjects completed the study. An audit of 29 subjects' records was conducted.
 - b. There were no limitations to this inspection.
 - c. No deviations were noted during the inspection.
 - d. Assessment of data integrity: There was a discrepancy noted between the — reports containing the primary efficacy endpoint and the data listing provided by the review division. The — reports gave the primary efficacy endpoint in whole number with no decimal points whereas the data listing provided by the review team gave numbers with decimal points. An example of this can be seen in the table below:

Subject	Group	Final ABPM per Data Listing	Baseline ABPM per Data Listing	Final ABPM per Report	Baseline ABPM per Report
527	Coreg 20mg	84.6	92.3	84	92

As seen in the table above, the — 24 hr ABPM reports which were sent directly to the sponsor during the course of the study, provided whole numbers for the DBP whereas the data listing provided by the review team for this inspection had numbers with decimal points in them. During the course of the study, the investigator uploaded the measurements taken by the ABPM device into a laptop computer and the data was then transmitted to — for analysis. Official — reports were then sent directly to the sponsor. It is unknown how the sponsor is reporting the primary efficacy endpoint to the FDA. The review division should be aware of the discrepancy noted above as this was found for all subjects at this site.

Overall, the study appears to have been conducted adequately. The review team will need to determine whether the discrepancy noted in the primary efficacy endpoint above impacts the overall efficacy for this site in support of the respective indication.

2. Steven Chrysant
Oklahoma Cardiovascular and Hypertension Center
5850 W Wilshire Blvd
Oklahoma City OK 7313

- a. At this site, 24 subjects were screened, 14 subjects were randomized and 14 subjects completed the study. There was no SAE reported for this site.
- b. There were no limitations to this inspection.
- c. The following deviation was noted during this investigation:

The clinical investigator did not adhere to the signed investigator statement and investigational plan [21 CFR 312.60]. Specifically, Subject 571 did not have a pharmacokinetic sample drawn prior to dosing at the up-titration visit 3; A pharmacokinetic sample for subjects 557, 560, 561, 568, 569, 570, 571, and 573 was not drawn 1-2 hrs post dose at up titration visit 3, A pharmacokinetic sample for subjects 553, 554, 559, 560, 569, and 573 was not drawn 4-8 hrs after dosing as specified in the protocol for the visit that occurred 5-7 days post visit 3; A pharmacokinetic sample was not drawn prior to subjects 553, 554, 557, and 559 receiving their final dose of medication at the end of treatment visit; Subjects 559, 560, and 561 did not have research visits within the protocol specified time periods; and Subjects 560, 571, 573, and 574 did not receive telephone contacts within the protocol specified time period after the last dose of medication.

- d. Assessment of data integrity: The same finding noted above concerning the discrepancy between ABPM values in the reports providing whole numbers and the data listing provided by the review division, providing numbers with decimal points was also found at this site.

Subject ID	Group	Final ABPM per Data Listing	Baseline ABPM per Data Listing	Final ABPM per Report	Baseline ABPM per Report
000553	80mg	⌈	99.4	⌈	98
000554	40mg		95.1		95
000557	20mg		102.9		102
000558	P		93.5		93
000559	P		88.6		88
000560	20mg		92.7		92
000561	80mg		97.7		97
000564	40mg		88.0		88
000568	20mg		90.6		90
000569	P		93.3		93
000570	80mg		94.3		94
000571	40mg		93.5		93
000573	40mg		97.4		97
000574	20mg		⌋		88.6

Overall, the study appears to have been conducted adequately. The review team will need to determine whether the discrepancy noted in the primary efficacy endpoint above impacts the overall efficacy for this site in support of the respective indication.

- 3. Larry I. Gilderman, D.O.
 1150 N University Dr.
 Pembroke Pines, FL 33024-5031

Page 5 of 6 - NDA 22-012 Coreg (carvedilol phosphate) controlled release capsules
 Summary Report of U.S Inspections

- a. At this site, 22 subjects were screened; 16 subjects were randomized, 7 subjects withdrew or terminated early, and 9 subjects completed the study. An audit of 22 subjects' records was conducted.
- b. There were no limitations to this inspection.
- c. No deviations were noted during the inspection.
- d. Assessment of data integrity: The same finding noted above concerning the discrepancy between ABPM values in the _____ reports providing whole numbers and the data listing provided by the review division, providing, numbers with decimal points was also found at this site.

Subject ID	Group	Final ABPM per Data Listing	Baseline ABPM per Data Listing	Final ABPM per Report	Baseline ABPM per Report
000942	Coreg 80mg		90.9		91
000943	Coreg 40mg		91.8		92
000944	Placebo		94.1		94
000946	Coreg 40mg		95.6		95
000947	Coreg 20 mg		93.2		93
000948	Coreg 80mg		93.6		93
000949	Coreg 20mg		91.9		91
000950	Placebo		92		92
000951	Coreg 40mg		93.2		93
000953	Coreg 20mg		100.3		100
000954	Placebo		89.8		89
000955	Coreg 80mg		102.1		102
000958	Coreg 80mg		103.7		103
000960	Coreg 20mg		92.3		92
000961	Coreg 40mg		101.3		101
000962	Placebo		93.3		93

Overall, the study appears to have been conducted adequately. The review team will need to determine whether the discrepancies noted in the primary efficacy endpoint above impacts the overall efficacy for this site in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general the sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigation. The inspection of documents support that audited subjects existed, signed informed consent prior to enrolling in the studies, and received assigned medications. The findings at Dr. Chrysant's site document violations regarding not following the investigational plan. The discrepancy noted above where the primary efficacy endpoint was reported as a whole number in the — , ABPM reports whereas the review division data listing reported the primary efficacy endpoint as numbers with decimal points, should be evaluated by the review division to determine whether or not this impacts the statistical significance of the data in support of this NDA. It was noted that sometimes the differences in values between the — reports and the data listings were problems noted with rounding of the numbers.

{See appended electronic signature page}

Dan-My T. Chu, Ph.D.
Regulatory Review Officer

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Dan-My Chu
7/31/2006 08:38:36 AM
UNKNOWN

Leslie Ball
8/8/2006 03:52:09 PM
MEDICAL OFFICER



NDA 22-012

DISCIPLINE REVIEW LETTER

SB Pharmco Puerto Rico Inc. d/b/a GlaxoSmithKline
Attention: Catherine K. Clark
One Franklin Plaza
200 N. 16th Street, FP1005
Philadelphia, PA 19102

Dear Ms. Clark:

Please refer to your December 21, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coreg (carvedilol phosphate) 10, 20, 40, and 80 mg Controlled Release Capsules.

A review by the Division of Medication Errors and Technical Support of your submission is complete, and we have the following comments:

A. GENERAL COMMENTS

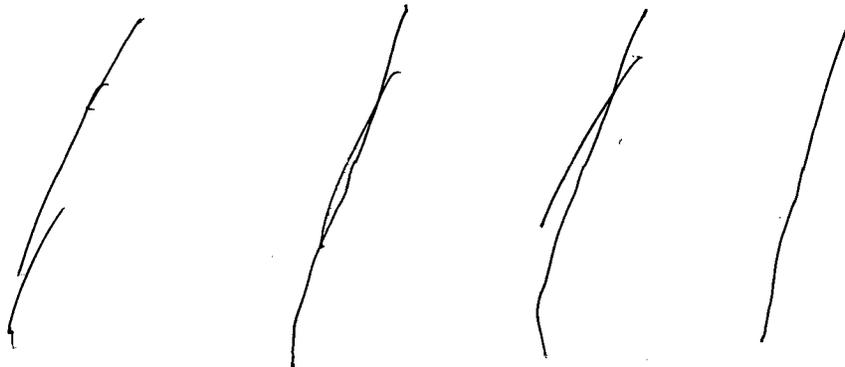
1. _____ is not an approved dosage form recognized by the USP. Currently the only two modified release dosage formulations are delayed-release and extended-release. You should revise your established name accordingly. The established name should be revised to read, "Carvedilol Extended-release Capsules" rather than _____ in order to ensure that practitioners are aware that the product is extended-release rather than immediate release.

2. Remove the _____

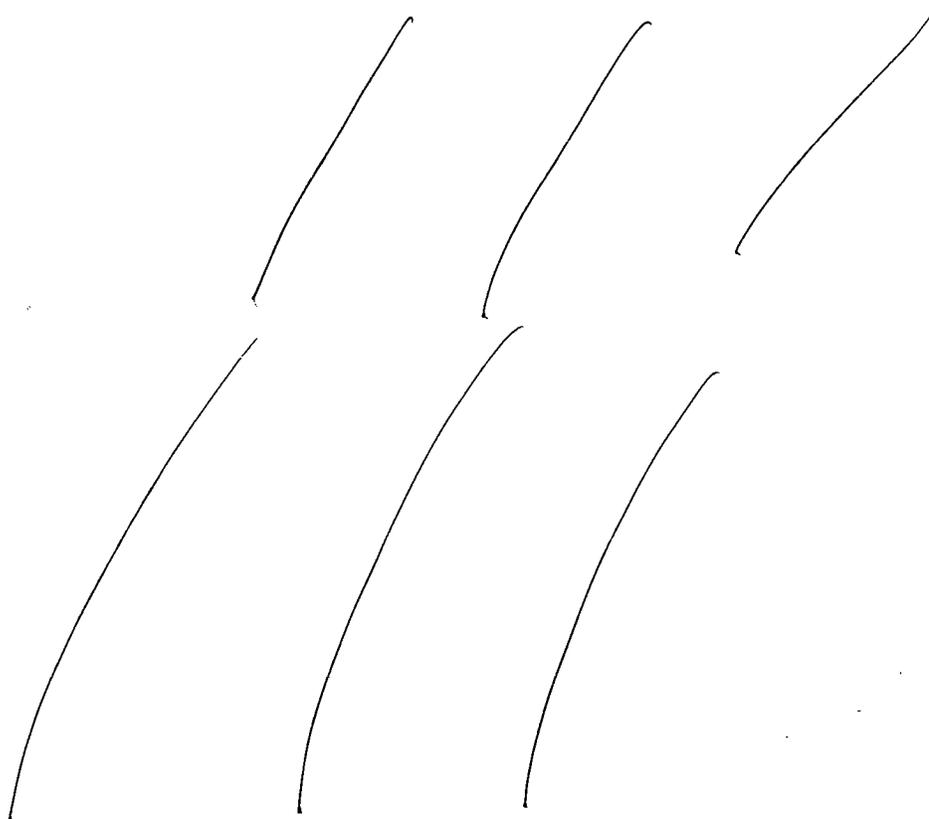


3. Th _____ 30-capsule and 90-capsule count bottles appear to be a unit-of-use container. Ensure that these containers utilize a child-resistant closure in accordance with the Poison Prevention Act.

4. _____



5. _____



We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Ms. Melissa Robb, Regulatory Health Project Manager, at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Melissa Robb
7/6/2006 09:18:34 AM
For Edward Fromm

MEMORANDUM

Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
WO 22, Mailstop 4447, HFD-420
Center for Drug Evaluation and Research

To: Norman Stockbridge, MD
Director, Division of Cardiovascular and Renal Products
HFD-110

From: Kristina C. Arnwine, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Through: Linda Kim-Jung, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

Date: May 12, 2006

Subject: OSE Consult 06-0033, Coreg CR (Carvedilol Extended-release Capsules) 10 mg, 20 mg, 40 mg, and 80 mg; NDA 22-012

This memorandum is in response to a January 31, 2006 request from your Division for a final review of the proprietary name, Coreg CR. The container label and package insert labeling were also provided for review and comment.

The proposed proprietary name was found acceptable by DMETS in ODS Consult 04-0236 dated February 11, 2005. In this review DMETS discussed post-marketing confusion and stated these issues would be addressed in a separate review. The addition of CR to Coreg does not pose additional concerns with the introduction of Coreg CR. Since the initial review of Coreg CR, DMETS has not identified any additional names with the potential for sound-alike and/or look-alike confusion with Coreg CR.

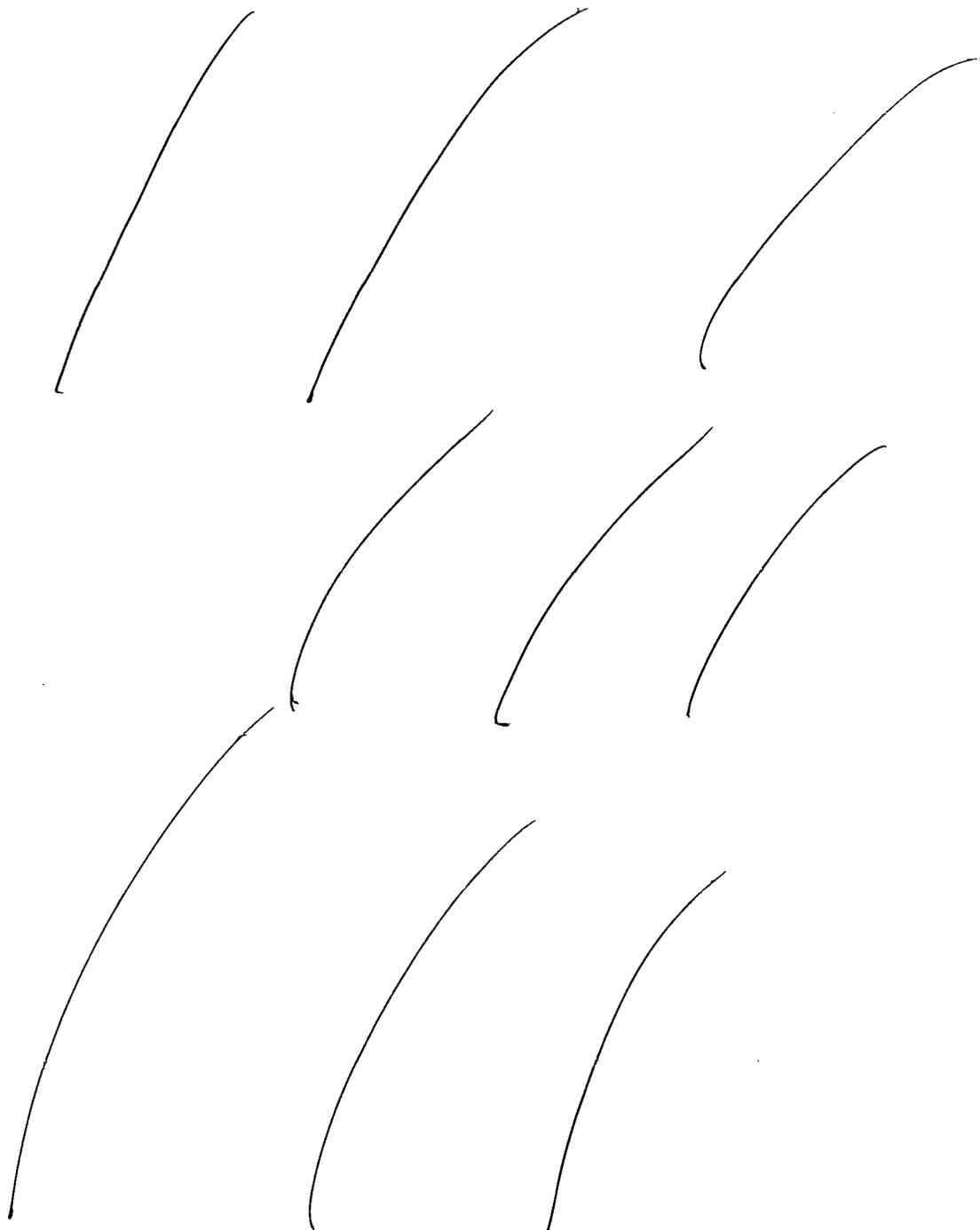
In the review of the container label and insert labeling of Coreg CR, DMETS acknowledges that the sponsor has addressed the label and labeling comments made previously in ODS Consult 04-0236. However, DMETS has identified the following areas of possible improvement, which might further minimize potential user error.

A. GENERAL COMMENTS

1. DMETS recommends consulting Guirag Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee (LNC), for guidance on the established name with respect to _____ d
_____ is not an approved dosage form recognized by the USP. Currently the only two modified release dosage formulations are delayed-release and extended-release. The sponsor should be instructed to revise their established name accordingly. Dependent upon the Labeling and Nomenclature Committee's decision, the established name should be revised to read, "Carvedilol Extended-release Capsules" rather than "_____" in order to ensure that practitioners are aware that the product is extended-release rather than immediate release.

2. Remove the _____

3. The  30 capsule and 90 capsule count bottles appear to be a unit-of-use container. Ensure that these containers utilize a child-resistant closure in accordance with the Poison Prevention Act.



In summary, DMETS has no objections to the use of the proprietary name, Coreg CR. We recommend implementation of the above label and labeling comments in order to minimize medication errors with the use of this product. Additionally, the Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the name Coreg CR acceptable from a promotional perspective. We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Diane Smith at 301-796-0538.

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/s/

Kristina Arnwine
6/2/2006 02:47:22 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
6/2/2006 02:55:19 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/2/2006 03:34:06 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/2/2006 04:07:00 PM
DRUG SAFETY OFFICE REVIEWER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-012 Supplement # N/A Efficacy Supplement Type SE- N/A

Trade Name: Coreg CR
Established Name: carvedilol phosphate
Strengths: 10, 20, 40, and 80 mg Capsules

Applicant: SB Pharmco Puerto Rico Inc. d/b/a GlaxoSmithKline
Agent for Applicant: Catherine Clark

Date of Application: December 21, 2005
Date of Receipt: December 21, 2005
Date clock started after UN: N/A
Date of Filing Meeting: February 9, 2006
Filing Date: February 19, 2006
Action Goal Date (optional): October 21, 2006 User Fee Goal Date: October 21, 2006

Indication(s) requested: treatment of essential hypertension, mild to severe chronic renal failure, and to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have left ventricular ejection fraction of less than/equal to 40% (with or without symptomatic heart failure).

Type of Original NDA: (b)(1) X (b)(2)
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain: NDA 20-297 Coreg (carvedilol) Tablets

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain: N/A

- If yes, has OC/DMPQ been notified of the submission? N/A YES NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain: N/A

- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format? Entire submission

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO

- Is it an electronic CTD (eCTD)? N/A YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, 3 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO

- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 27,114 and 70,154

- End-of-Phase 2 Meeting(s) Date(s) August 25, 2004 and September 22, 2004 NO
(CMC)

If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s) Date(s) July 21, 2005 and June 15, 2005 (CMC) NO
If yes, distribute minutes before filing meeting

Project Management

- Was electronic "Content of Labeling" submitted? YES NO
If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO

- Risk Management Plan consulted to ODS/IO? N/A YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO

- Has DOTCDP been notified of the OTC switch application? N/A YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
N/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? N/A YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? N/A YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? N/A YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 9, 2006

BACKGROUND: NDA 20-297, Coreg (carvedilol), is currently approved as an immediate release formulation for the treatment of essential hypertension, mild to severe congestive heart failure, and to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of <40%. For all three indications, carvedilol is to be taken twice daily.

The sponsor submitted NDA 22-012, Coreg CR (carvedilol phosphate), on December 21, 2005. This formulation will require once daily dosing. The sponsor is seeking approval for the same indications for which the immediate release formulation is approved.

ATTENDEES:

Norman Stockbridge, M.D., Ph.D.	Director Division of Cardiovascular and Renal Products
Ellis Unger, M.D.	Deputy Director Division of Cardiovascular and Renal Products
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Clinical Division of Cardiovascular and Renal Products
Albert DeFelice, Ph.D.	Team Leader, Pharmacology Division of Cardiovascular and Renal Products
Christine Garnett, Pharm.D.	Pharmacometrics
Kasturi Srinivasachar, Ph.D.	Pharmaceutical Assessment Lead Division of Pre-Marketing Assessment 1
John Lawrence, Ph.D.	Team Leader, Statistics Division of Biometrics 1
Steven Bai, Ph.D.	Statistician Division of Biometrics 1
Edward Fromm	Chief, Project Management Staff Division of Cardiovascular and Renal Products
Akinwole Williams, M.D.	Medical Officer Division of Cardiovascular and Renal Products
Melissa Robb	Regulatory Health Project Manger Division of Cardiovascular and Renal Products

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline</u>	<u>Reviewer</u>	<u>Due</u>
Medical:	Akinwloe Williams, M.D.	8/30/06
Secondary Medical:	Abraham Karkowsky, M.D., Ph.D (if needed)	
Statistical:	Steven Bai, Ph.D.	4/30/06
Chemistry:	Not yet decided	9/21/06
Biopharmaceutical:	Christine Garnett, Pharm.D.	9/15/06
Regulatory Project Management	Melissa Robb	

Per reviewers, are all parts in English or English translation?
If no, explain:

YES NO

CLINICAL		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• Clinical site inspection needed?		YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
• Advisory Committee Meeting needed?	YES, date if known _____		NO <input checked="" type="checkbox"/>
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?		N/A <input type="checkbox"/>	YES <input type="checkbox"/> NO <input type="checkbox"/>
CLINICAL MICROBIOLOGY	N/A <input checked="" type="checkbox"/>	FILE <input type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
STATISTICS	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
BIOPHARMACEUTICS		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• Biopharm. inspection needed?		YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
PHARMACOLOGY	N/A <input checked="" type="checkbox"/>	FILE <input type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• GLP inspection needed?		YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
CHEMISTRY		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• Establishment(s) ready for inspection?		YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
• Microbiology		YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3. Convey document filing issues/no filing issues to applicant by Day 74.

Melissa Robb
Regulatory Project Manager, HFD-110

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Melissa Robb
3/2/2006 10:33:22 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-012

SB Pharmco Puerto Rico Inc. d/b/a GlaxoSmithKline
Attention: Ms. Catherine K. Clark
One Franklin Plaza
200 N. 16th Street
Philadelphia, PA 19102

Dear Ms. Clark:

Please refer to your December 21, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coreg (carvedilol phosphate) Controlled Release 10, 20, 40, and 80 mg Capsules.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on February 19, 2006 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues and request that you submit the following information:

1. Please submit the following data to support the population PK-PD analyses for studies 367, 369, 395, 908, and 902:

- All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- A model development decision tree and/or table which gives an overview of modeling steps.

2. Please submit all dissolution data to support the alcohol interaction.

NDA 22-012

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We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardio-Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Norman Stockbridge
2/16/2006 03:21:38 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-012

NDA ACKNOWLEDGMENT

SB Pharmco Puerto Rico Inc.
d/b/a GlaxoSmithKline
Attention: Ms. Catherine K. Clark
One Franklin Plaza
200 N. 16th Street, FP1005
Philadelphia, PA 19102

Dear Ms. Clark:

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

Name of Drug Product:	Coreg®CR (carvedilol phosphate)-10,-20-, 40, and 80 mg Controlled Release Capsules
Review Priority Classification:	Standard (S)
Date of Application:	December 21, 2005
Date of Receipt:	December 21, 2005
Our Reference Number:	NDA 22-012

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 19, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 21, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

NDA 22-012

Page 2

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products, Room 4167
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Edward Fromm
2/2/2006 10:36:08 AM

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).

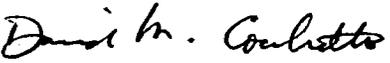
Please mark the applicable checkbox.

- (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	(See Attached List)	

- (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 David M. Cocchetto	TITLE Vice Pres., U.S. Regulatory Affairs
FIRM / ORGANIZATION GlaxoSmithKline	
SIGNATURE 	DATE December 14, 2005

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

**PRESCRIPTION DRUG USER FEE
COVERSHEET**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>SB PHARMCO PUERTO RICO INC DBA GLAXOSMITHKLINE James McCarthy 200 North 16th Street 1 Franklin Plaza Philadelphia PA 19101 US</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>22-012</p>
<p>2. TELEPHONE NUMBER</p> <p>215-751-5923</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p>

<p>3. PRODUCT NAME</p> <p>Coreg CR (carvedilol phosphate controlled release)</p>	<p>6. USER FEE I.D. NUMBER</p> <p>PD3006345</p>
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7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<p><input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)</p>	<p><input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE</p>
<p><input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act</p>	<p><input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY</p>

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

<p>Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448</p>	<p>Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852</p>	<p>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.</p>
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<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p> <p><i>David M. Gochetto</i></p>	<p>TITLE</p> <p>Vice President, U.S. Regulatory Affairs</p>	<p>DATE</p> <p>December 9, 2005</p>
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9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION

\$767,400.00

Minutes of a Meeting
July 21, 2005

Drug: Carvedilol phosphate Modified Release Capsules
IND: 70,154
Sponsor: SmithKline Beecham d/b/a GlaxoSmithKline.

Date Requested: April 7, 2005
Date Confirmation Faxed: April 11, 2005
Rescheduled per Sponsor: June 7, 2005

Type: Pre-NDA
Classification: B

FDA Participants:

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Acting Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Thomas Marciniak, M.D.	Team Leader, Clinical, HFD-110
Salma Lemtouni, M.D., M.P.H.	Medical Officer, HFD-110
Jogarao Gobburu, Ph.D.	Team Leader, Pharmacometrics, HFD-860
Christine Garnett, Pharm.D.	Pharmacometrics, HFD-860
Kris Raman, Ph.D.	Chemist, HFD-810
Melissa Robb	Regulatory Health Project Manager, HFD-110

Sponsor Participants:

Linda Henderson, Ph.D.	Director, Clinical Pharmacology and Discovery Medicine
Charlotte Baidoo, MMath	Senior Statistician, Biomedical Data Sciences
Catherine K. Clark	Clinical Pharmacology Statistics and Programming
Duane A. Boyle, Pharm.D.	Director, US Regulatory Affairs - Cardiovascular
Malini Iyengar, Ph.D.	Director, Clinical Pharmacokinetics
Clare Kahn, Ph.D.	Principal Statistician, Clinical Pharmacology and Discovery Medicine
Mary Ann Lukas, M.D.	Vice President, US Regulatory Affairs, Cardiovascular, Urogenital, Metabolic
Choon K. Oh, Ph.D.	Senior Director, Medicine Development Center - Cardiovascular
Elizabeth Tarka, M.D.	Director, Pharmaceutical Development
David M. Tenero, Pharm.D.	Director, Medicine Development Center-Cardiovascular
Nevine Zariffa, MMath	Director, Clinical Pharmacokinetics
	Therapy Area Director, Cardiovascular and Metabolism, Biomedical Data Sciences

Background:

Carvedilol is currently approved as an immediate release formulation for the treatment of essential hypertension, mild to severe congestive heart failure, and to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of $\leq 40\%$. For all three indications, carvedilol is to be taken twice daily. The sponsor is developing a new formulation that has controlled-release (CR) characteristics and would allow for once daily dosing. The sponsor has met previously with the Division to discuss the development of a CR formulation on April 30, 2003, August 6, 2003, November 25, 2003, and May 24, 2004. An End of Phase 2 (EOP2) meeting was held with the Division to discuss clinical issues on August 25, 2004 and Chemistry,

Manufacturing, and Controls (CMC) development issues on September 22, 2004. A Pre-NDA CMC meeting was held with the Division on June 15, 2005.

Meeting:

Dr. Raman began by stating that the word "micropump" can not be included as the established name. The approved USAN name for the drug substance is carvedilol phosphate. The sponsor stated that they plan to use the name pending final approval from the Agency, as the established name for this modified release formulation of carvedilol. The sponsor does not intend to use the words "micropump" or "microparticle" to describe the drug product in marketing, although they do describe the drug substance as microparticles. Dr. Raman believed the term "microparticles" for descriptive purposes with the drug substance was acceptable, but he stated he would confirm this with his supervisor.

The sponsor then presented a brief summary of Study 369 designed to support the use of Coreg CR in patients with congestive heart failure and post-MI with left ventricular dysfunction (See Appendix A). Dr. Karkowsky inquired if the active metabolite, described in the package insert as being 13-fold more potent than the parent as a beta-blocker, was measured in this trial. The sponsor stated that it was not. The sponsor stated that the in vivo data were collected in rabbits and they are unsure of how those data would relate to humans. In addition, the active metabolite has the same time course as the parent compound. Dr. Stockbridge asked that this issue be addressed in the submission.

The sponsor then presented the rationale for their comparison of the pharmacokinetic (PK) and pharmacodynamic (PD) properties of the immediate release (IR) and CR formulations of carvedilol (See Appendix B). Dr. Marciniak inquired where the data to establish the model for the IR formulation were obtained. The sponsor stated it was data from steady-state levels in patients with hypertension. This trial had 36 patients. This was the only trial that the sponsor had data from both the AM and PM dosing. It is important to have data from two doses, as they have learned that the peak from the second dose is not as high as the first dose. The sponsor plans to use the data from Study 902, also a hypertension study, to validate this model. Dr. Karkowsky was concerned that since the results are not linear, as is seen with plasma concentrations, the results may be harder to interpret. The sponsor believes that PK data are a more sensitive measure of effectiveness than PD data. Dr. Karkowsky was concerned that some of the indications that will be "transferred" to the CR formulation of Coreg from the IR formulation based on PK and PD data will be for indications that are not titratable. Therefore, the proposed 30% margin is somewhat worrisome. The sponsor clarified that they plan to use a 20% margin, which they believe is achievable in most cases. However, in some instances, where more variability is introduced into the model, they believe the analysis of the IR vs. IR will support a 30% margin.

Dr. Stockbridge stated that when the Division discussed these issues in an internal meeting, many of the same ideas were presented, including the important features of a PK/PD model. The Division believes that the following features are critical in the CR vs. IR comparison: the PD data should be collected in a target population, an 80-125% log-transformed AUC ratio should be used, the Cmin of the CR formulation should be at least as high as Cmin of the IR formulation, and the trough to peak ratio in the CR formulation should not be larger than the trough to peak ratio seen in IR formulation. The sponsor believes that it is unlikely that the Cmin of the CR formulation will be more than 10% lower than that of the IR formulation. Dr. Garnett requested the sponsor clarify their definition of Cmin. The sponsor stated that they are using the concentration 24 hours after dosing. The sponsor stated that there is very little lag time due to approximately 1/3 of the CR formulation being composed of an IR component. In addition, the Division is interested in the inter- and intra-subject variability in Cmax and AUC. The sponsor presented a slide showing that the intra-subject variability (based on data from two different studies, one using each formulation of carvedilol) appears to be better with the CR formulation (See Appendix C). The data for the CR formulation was collected using Study 906 which was a replicate design. The data for the IR formulation was from Study 271, in which patients were fasting. The sponsor confirmed that they have performed a food effect study, but are still awaiting results.

The sponsor described their proposed analysis strategy outlined in Table 8 (Proposed Multi-Stage Analysis Strategy) of their briefing document. The Division believes they have a PD analysis plan that is much simpler than that presented by the sponsor. The Division does not believe it is necessary to use a model from healthy and hypertensive patients to project PD data in the CHF population (study 369). The Division believes it would be better to use the observed PD data from the hypertensive study (902), where PD data from both formulations were collected in the same patient. Then the observed PD effects can be compared. In addition, these data could be used to characterize the concentration-effect relationship. The concentration-effect models for the IR and CR formulations, together with the PK data from study 369 and observed PD data from study 902, could be used as a basis for approval. The sponsor stated that due to the timing of BETs in study 902, there is only one timepoint (predose BET) in which PD data were collected in all patients. Dr. Gobburu stated that this would be acceptable. Dr. Gobburu said that this analysis should be the primary analysis. Additional analyses described earlier would be considered supportive. The sponsor was concerned that Study 902 was not designed to be analyzed in that way. The sponsor stated that the trial was designed to use a population PK-PD modeling approach to compare formulations. However, the sponsor was unsure if the observed PD data would reveal a difference greater than 20%, as they have not yet looked at the data. The sponsor added that as they begin to look at the data, the model may change, but wanted to know if the strategy described was acceptable to the Division. The Division stated that the sponsor has to demonstrate that the concentration-beta blockade relationships for the two formulations are the same. The sponsor stated that an overlay of the concentration-beta blockade data from the two formulations is almost identical. The Division believed this would be very helpful.

The sponsor summarized some of the aspects of the PD analysis. The goal of the hypertension study would be to show that both the point estimate and the confidence interval for PD_{min} of the two formulations are similar. The sponsor believes that they can probably show a $\leq 10\%$ difference in the point estimate; however, they will not be able to illustrate bioequivalence. The Division believes that this plan is not unreasonable and concedes that this is an unusual situation. The sponsor will provide data that the PK/PD relationship is not related to the formulation's properties.

The sponsor then presented a brief summary of the Study 367, hypertension (See Appendix D). The Division inquired if the patients were genotyped for 2D6. The sponsor stated that patients were requested to provide samples for analysis, but this was not required. The Division is not concerned with the stated primary endpoint. The Division is concerned with the time course of effect, an effect throughout the interdosing interval, and the peak to trough ratio. The sponsor may win on the primary endpoint, but still not provide enough evidence to convince the Agency that the two formulations are similar enough.

Questions:

1. We propose to include individual study reports. We are not planning to provide integrated summaries of efficacy or safety since the total number of relevant studies supporting the proposed indications, in general, is small and does not warrant study integration. In addition, only one study (study 367 in essential hypertension) addresses efficacy of Coreg CR making integration not feasible. Reports of individual studies will serve to describe safety and efficacy. Is the agency in agreement?

The Division agreed.

2. We plan to provide patient case report forms for deaths and withdrawals due to adverse events upon request from the Division rather than submitting them in the initial application. Does the Agency agree with this approach?

The Division did not agree. Case report forms (CRFs) for deaths and withdrawals due to adverse events should be submitted with the initial application. These CRFs should contain all data, doctor's notes, and hospital records that are appropriate. Dr. Stockbridge added that any other CRFs requested during the review of the application should be submitted within a reasonable amount of time.

3. For patients who consented but failed Screening for studies due to an SAE or Death, we plan to provide only a listing by study with reason(s) identified. Does the agency require any further information on these patients?

The sponsor confirmed that none of the patients who failed screening were exposed to drug. In that case, the Division agreed.

4. In study 367 which will characterize the effect of various doses of Coreg CR on blood pressure reduction, GSK plans to compute the change from baseline in trough:peak ratio for DBP and SBP via ABPM, by the following method: $100\% \times \{(\text{mean DIF of active trough} - \text{mean DIF of placebo trough}) / (\text{mean DIF of active peak} - \text{mean DIF of placebo peak})\}$ where DIF = value at study endpoint minus value at baseline for each subject. Is the agency in agreement with the method?

The Division is interested in evaluating the time course of drug effect using both systolic and diastolic blood pressures and ensuring that the effect lasts the entire interdosing interval. The Division is not concerned how the formal calculation of the peak to trough ratio is performed. In addition, the Division will be evaluating intersubject variability, drug effect, and time course. The sponsor confirmed that they will have ABPM data by subject. The Division will be interested in evaluating hourly means and individual patient data by subtracting patient's on-treatment values from values collected on the baseline day. The Division believed it may be helpful for the sponsor to include hourly averages in their submission. The sponsor suggested submitting graphical displays by subject also. In addition, the sponsor will submit hourly means by subject within a dose group and hourly means for dose groups and individuals. The Division agreed that these analyses will be helpful when reviewing the application.

5. In study 367, exploratory covariate/subgroup analyses for the primary efficacy variable (i.e., mean change from baseline in DBP measured by 24 hr ABPM) are planned for the following prognostic and demographic characteristics: gender, race (Caucasian, African American, other), age (<65, >= 65), BMI (<27, >= 27) and diabetes status at baseline (yes, no). Does the agency agree with the above list?

The Agency agreed, but reminded the sponsor about the analysis of 2D6 patients discussed earlier, if possible.

6. In study 367, the planned analyses of secondary efficacy variable assessments of SBP via ABPM include:
Change from baseline in mean SBP measured at the drug-trough blood levels (20-24 hrs)

Change from baseline in mean SBP in the morning, afternoon and at night
Does the agency agree with the above SBP assessments?

The Division agreed and added that these will help the Division evaluate the time course of the drug. The Division also believed it would be helpful for the sponsor to evaluate the plasma concentration responsible for a blood pressure effect with CR vs. IR. The sponsor stated that there will not be any IR data collected to do this analysis in this trial. In addition, the sponsor believes it is difficult to develop a concentration response with beta-blockers. The Division agreed.

7. In addition to the standard adverse event displays for study 367, GSK plans to produce emergent adverse event summaries by demographic subgroups of gender, race (Caucasian, African American, other) and age (<65, >= 65), provided none of these subgroups contain less than 10% of the population being represented. Will these summaries be sufficient to allow the agency to review safety data for this file?

The sponsor confirmed that they will be submitting all raw data for review. In that case, the Division agreed.

8. We solicit FDA's agreement on the proposed strategy for assessing the similarity of the Coreg IR formulation with the Coreg CR formulation. With FDA's agreement to this proposed strategy, GSK will complete all the simulation work to assess the robustness of the modeling and simulation procedure (see below) and establish final threshold margins for the supportive analyses.

Scenarios completed to date

1. Evaluation of the number of simulated studies per scenario
2. Impact of the size of the residual PD variability
3. Impact of the size of the within-subject variability for oral clearance
4. Impact of the size of the residual PK variability
5. Sensitivity analysis of Emax
6. Impact of decreased oral clearance in Class III and IV CHF
7. Impact of decreased oral bioavailability for one IR administration

Other scenarios planned for evaluation

1. Impact of a modest difference in variability (i.e., 5%) for one IR administration
2. Sensitivity analysis of other PK and PK/PD parameters and corresponding between-subject variability estimates
3. Sensitivity of inclusion of correlation between Emax and E0
4. Impact of alternative PK/PD model (log-linear)

The answer to this question has already been discussed above.

9. GSK proposes to submit blinded SAE data in line-listings format for the ongoing Phase IIIB Coreg CR (Left Ventricular Hypertrophy and Microalbuminuria) studies. Does the Agency agree with this approach?

The Division agreed.

10. Does the Agency require GSK to submit blinded SAE data in line-listings format for the ongoing

The Division stated that the sponsor should share all information they have available with the Agency in the application.

Addendum to Meeting Minutes from the Office of Drug Safety

- If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).
- If the NDA/BLA application includes RiskMAPs or pharmacovigilance plans and will be submitted in the Common Technical Document format, please submit as follows:

RiskMAPs

2.5.5 Overview of Safety with appropriate cross references to section
2.7.4 Summary of Clinical Safety
and any other relevant sections of the Common Technical Document for the NDA/BLA application.

Pharmacovigilance plans

2.5.5 Overview of Safety, with any protocols for specific studies provided in 5.3.5.4 Other Clinical Study Reports or other sections as appropriate
(e.g., module 4 if the study is a nonclinical study).

If the application is not being submitted as a Common Technical Document, include proposed RiskMAPs in the NDA Clinical Data Section (21 CFR 314.50 (d)(5)) or BLA Clinical Data Section (21 CFR 601.25(b)(3)) and clearly label and index them.

- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

Premarketing Risk Assessment: <http://www.fda.gov/cder/guidance/6357fnl.htm>

Development and Use of Risk Minimization Action Plans:
<http://www.fda.gov/cder/guidance/6358fnl.htm>

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:
<http://www.fda.gov/cder/guidance/6359OCC.htm>

- If there is any information on product medication errors from the premarketing clinical experience, ODS requests that this information be submitted with the NDA/BLA application.
- The sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

Signature, minutes preparer: {See appended electronic signature page}

Concurrence Chair: *{See appended electronic signature page}*

Drafted: 7/25/05

Finaled: 8/2/05

RD:

Stockbridge	8/2/05
Karkowsky	8/1/05
Marciniak	7/29/05
Lemtouni	7/29/05
Gobburu	7/29/05
Garnett	7/29/05
Raman	7/29/05

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Draft Labeling

Deliberative Process

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/s/

Melissa Robb
8/2/05 09:10:13 AM

Norman Stockbridge
8/2/05 09:26:39 AM

June 15, 2005

Drug: Coreg (carvedilol phosphate) CR Capsules
IND: 70,154
Sponsor: SmithKline Beecham Corporation d/b/a GlaxoSmithKline

Date Requested: April 13, 2005
Date Confirmation Faxed: April 22, 2005

Type: Pre-NDA, CMC
Classification: B

FDA Participants:

Kasturi Srinivasachar, Ph.D. Team Leader, Chemistry, HFD-810
Kris Raman, Ph.D. Chemist, HFD-810
Lydia Velazquez, Pharm.D. Pharmacokineticist and Biopharmaceutist, HFD-860
Melissa Robb Regulatory Health Project Manager, HFD-110

Sponsor Participants:

Scott Ziegenfuss Assistant Director, CMC Regulatory Affairs
Choon Oh Director, Pharmaceutical Development
Grant Spoor Team Manager, Chemical Development, Synthetic Chemistry
Tom Cacchio Principal Scientist, Chemical Development, Analytical Sciences
Catherine Clark Director, US Regulatory Affairs - Cardiovascular
Robert Carlton Investigator, Physical Properties and Developability, Pharmaceutical Development

Background:

Carvedilol is currently approved as an immediate release formulation for the treatment of essential hypertension, mild to severe congestive heart failure, and to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of $\leq 40\%$. For all three indications, carvedilol is to be taken twice daily. The sponsor is developing a new formulation that has modified-release (MR) characteristics and would allow for once daily dosing. The sponsor has met previously with the Division to discuss the development of a MR formulation on April 30, 2003, August 6, 2003, November 25, 2003 and May 24, 2004. An End of Phase 2 (EOP2) meeting was held with the Division to discuss clinical issues on August 25, 2004 and Chemistry, Manufacturing, and Controls (CMC) development issues on September 22, 2004.

Meeting:

Drug Substance:

1. Particle Size Specification: Is FDA amenable to this plan?

The sponsor began by stating that since the EOP2 meeting held with the Division in September 2004, they no longer believe that control of API particle size is essential. The sponsor plans to conduct experiments to test this hypothesis and present this data in the NDA submission. If the data supports this hypothesis, the sponsor plans to include an argument in the NDA submission that a specification is not needed. However, if the data does not support this hypothesis, the sponsor will use the data to justify the specifications chosen. Dr. Srinivasachar inquired about the studies planned by the sponsor to support this hypothesis. Dr. Srinivasachar stated that it would be difficult to prove that no specification is needed, as the tablet does not fully dissolve. He believes it may be more prudent to have a wide specification, if the data can support it. The sponsor agreed that this hypothesis may be difficult to prove. The sponsor is planning to use the largest particle sizes currently available

and compare the dissolution of drug product batches made with these with that of the pivotal batches. Dr. Srinivasachar was concerned that at a later date the sponsor may use a larger particle size. In that case, he was unsure if it would be possible to extrapolate the data. This data may result in limiting the particle size to the largest particle size studied. The sponsor added that they _____

The sponsor confirmed that they are in agreement with setting a specification on heavy metals for the drug substance.

Dr. Srinivasachar noted that the sponsor is planning to : _____

Drug Product:

2. Batch Records and Dissolution Data in the NDA: Does FDA concur?

The Division concurred with the sponsor's plan to submit one executed batch record for a single batch that was used in both the pivotal clinical and primary stability studies in their NDA submission. The sponsor noted that one batch record is fully representative of the manufacturing process for all strengths, as all strength capsules are filed with the same microparticles in the same ratio, the only difference being the amount of the fill and the capsule shell color and size.

Dr. Velazquez added that the sponsor's plan to provide dissolution data for all pivotal clinical and primary stability batches with the NDA submission was acceptable.

Dr. Srinivasachar noted that sponsor had in their original briefing package a question about _____

_____. Therefore, this is no longer an issue.

3.

4. Primary Stability Data for the NDA: GSK also requests to submit _____ data in the NDA on the additional _____ described in Section 4.1 above.
Does FDA concur?

Dr. Srinivasachar agreed that the sponsor can submit _____ data on the new packaging presentations _____ that have been placed on stability with the NDA

submission. The sponsor will submit _____ data on all other presentations, as discussed previously at the EOP2 meeting with the NDA submission.

5. Primary Stability Data for the NDA: GSK requests to submit the _____ data for all packs within 6.5 months after the NDA filing, without impacting the NDA review period. Does FDA concur?

The Division agreed, but requested the data be submitted as soon as possible.

6. Primary Stability Data for the NDA: Assuming the acceptance of the questions above, GSK proposes to submit a statistician's package in the _____ stability data amendment and not in the original NDA. Does FDA concur?

The Division agreed. Dr. Srinivasachar noted that it appears the sponsor is planning to extrapolate stability data and informed the sponsor that the Agency follows ICH guidelines.

7. Microparticle manufacturing facility: Does FDA concur with this plan regarding PAI readiness at the proposed commercial secondary manufacturing site by the end of January 2006 (approximately 1.5 months after NDA submission)?

The sponsor stated that a commercial-scale manufacturing building is being constructed on the same campus, utilizing identical or equivalent equipment, and the same personnel and quality systems as the building in which the pivotal and primary batches were manufactured. Although the building will be ready in _____ two of the protocols, _____ will not be executed until January 2006. Dr. Srinivasachar did not think this would be an issue provided the date of PAI readiness is not extended, but stated he would need to discuss this further with compliance. Dr. Srinivasachar stated that when a NDA is submitted, the information for inspections is entered in a database. If the facility has a registration number, he thought there would be no reason that this data could not be entered and inspections scheduled for some time after January 2006. Dr. Srinivasachar will confirm this with compliance and follow-up with the sponsor.

Dr. Velazquez stated that this change is defined as a SUPAC Level 2 change. Therefore, the sponsor would need to provide dissolution data from the commercial batches with a comparison to the biobatches, batches used in any studies essential to support approval. In addition, the sponsor would need to provide a F2 similarity factor. The sponsor inquired if this data could be submitted with the first annual report. Dr. Velazquez stated that this information would need to be submitted and reviewed prior to NDA approval. Dr. Velazquez stated that it would be acceptable to submit this data no later than 6.5 months after NDA submission. The sponsor inquired if they could submit dissolution data on the highest strength of the commercial batches. Dr. Velazquez stated that would be acceptable (see NOTE below), provided it was using full manufacturing scale. Dr. Velazquez requested that when the sponsor submitted the amendment with the dissolution data from the commercial batches a table be included with batch numbers for the biobatches and the commercial batch. This table should include batch numbers, expiration dates, lot numbers, and size so that one could cross reference a

_____ trials.

The sponsor wanted to confirm that this would be acceptable and that the Agency would accept dissolution data from this batch as a "commercial batch" even if none of the batch was sold commercially. Dr. Velazquez stated that it would be acceptable provided it was manufactured in the new facility.

NOTE: Upon further consultation with the Division of Pharmaceutical Evaluation I, the dissolution tests discussed earlier would have to be performed with every strength. Conducting dissolution studies on the highest strength and waiving down the need for such studies with the lower strengths will not be possible. The sponsor has been informed and they agree to perform the required studies via e-mail through Dr. Scott Ziegenfuss on June 23, 2005.

The sponsor inquired if _____ accelerated stability data would be required as this change is defined as SUPAC Level 2 change. Dr. Srinivasachar stated that this data may not be essential. The sponsor stated they would include this data in the annual report and be prepared to provide it earlier, during the NDA review, if requested.

/ / / / / / /

The sponsor inquired about the validation batches required. The sponsor is planning on doing _____ validation batches on each of the microparticles (carvedilol phosphate immediate release microparticles, carvedilol phosphate CR _____). The sponsor requested to do _____ validation batches on the low dose (10 mg) and the high dose (80 mg), but do only _____ on the 20 and 40 mg strengths. The Division stated that this plan would be acceptable.

The sponsor inquired about the requirements if there was a change in manufacturing equipment. Dr. Srinivasachar stated that it is dependant on the type of change and referred the sponsor to the SUPAC guidance.

The sponsor inquired about the requirements if there was a change in formulation. Dr. Velazquez stated that this is also dependant on the degree of change. Some changes would require bioequivalency to be demonstrated. _____

Signature, minutes preparer: {See appended electronic signature page}

Concurrence Chair: {See appended electronic signature page}

Drafted: 6/21/05

Finaled: 7/7/05

RD:

Srinivasachar 7/7/05

Raman 7/7/05

Velazquez 6/23/05

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/s/

Melissa Robb
7/7/05 01:32:41 PM

Kasturi Srinivasachar
7/7/05 02:53:35 PM

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 Draft Labeling

 Deliberative Process

September 22, 2004

Drug: Carvedilol Phosphate Micropump Modified Release Capsules
IND: 70,154
Sponsor: GlaxoSmithKline

Date Requested: August 3, 2004
Date Confirmation Faxed: August 10, 2004
Briefing Package Received: August 26, 2004

Type: EOP2 CMC
Classification: B

FDA Participants:

Kasturi Srinivasachar, Ph.D. Chemistry Team Leader, HFD-810
Kris Raman, Ph.D. Chemist, HFD-810
Lydia Velazquez, Pharm.D. Pharmacokineticist and Biopharmaceutist, HFD-860
Melissa Robb Regulatory Health Project Manager, HFD-110

Sponsor Participants:

Scott Ziegenfuss Assistant Director, CMC Regulatory Affairs
Choon Oh Director, Pharmaceutical Development
Grant Spoons Team Manager, Chemical Development, Synthetic Chemistry
Tom Cacchio Principal Scientist, Chemical Development, Analytical Sciences
Alireza Kord Director, Analytical Sciences
Dale Stockbower Director, CMC Regulatory Affairs
Catherine Clark Director, US Regulatory Affairs - Cardiovascular

Background:

Carvedilol is currently approved as an immediate release formulation for the treatment of essential hypertension, mild to severe congestive heart failure and to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of $\leq 40\%$. For all three indications, carvedilol is to be taken twice daily. The sponsor is developing a new formulation that has modified-release (MR) characteristics and would allow for once daily dosing. The sponsor has met previously with the Division to discuss the development of a MR formulation on April 30, 2003, August 6, 2003, November 25, 2003 and May 24, 2004. An End of Phase 2 meeting was held with the Division to discuss clinical issues on August 25, 2004. The sponsor requested this meeting to reach agreement with the Agency regarding specific Chemistry, Manufacturing, and Controls (CMC) development issues.

Meeting:

Drug Substance

1. GSK believes that the data described in Part I, Section 2 adequately demonstrate proof of structure of carvedilol phosphate, as the hemihydrate, to support product registration. Does FDA concur?

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Melissa Robb
10/4/04 09:51:43 AM

Kasturi Srinivasachar
10/4/04 06:38:10 PM

End of Phase II Meeting Minutes

Meeting Date: August 25, 2004
Type of Meeting: EOP2 Meeting
P-IND Application: 70,154
Sponsor: GlaxoSmithKline
Classification: B
Meeting Request Date: July 15, 2004
Confirmation Date: July 16, 2004 (faxed confirmation sent)
Briefing Package Received: August 6, 2004
Meeting Chair: Robert Temple, M.D.
Meeting Recorder: Dianne C. Paraoan

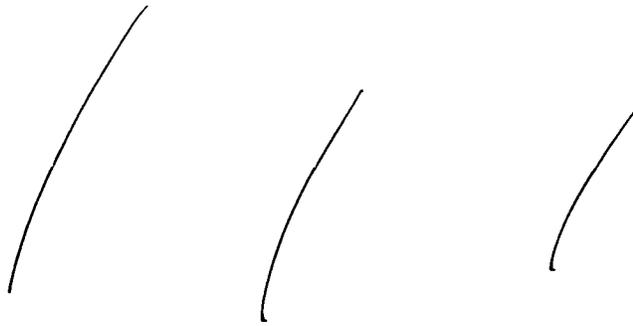
Attendees:

Division of Cardio-Renal Drug Products

Robert Temple, M.D.	Director, Office of Drug Evaluation I, HFD-101
Norman Stockbridge, M.D., Ph.D.	Acting Director, Division Cardio-Renal Drug Products, HFD-110
Thomas Marciniak, M.D.	Acting Deputy Director, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical Officer, HFD-110
Salma Lemtouni, M.D., MPH	Medical Officer, HFD-110
Mehul Desai, M.D.	Medical Officer, HFD-110
John Lawrence, Ph.D.	Statistician, HFD-710
Jogarao Gobburu, Ph.D.	Team Leader, Pharmacometrics, HFD-860
Lydia Velazquez, Pharm.D.	Clinical Pharmacologist, HFD-860
Dianne C. Paraoan	Regulatory Health Project Manager, HFD-110

GlaxoSmithKline

Charlotte Baidoo	Senior Statistician, Clinical Pharmacology Statistics and Programming
Catherine Clark	Director, US Regulatory Affairs-Cardiovascular
Duane Boyle, Ph.D.	Director, CVU, Clinical Pharmacokinetics/Modeling & Simulation
Mary Ann Lukas, M.D.	Senior Director, Medicine Development Center-Cardiovascular
Ruth Ann Subach, Pharm.D., BCPS	Manager, Clinical Pharmacology, Cardiovascular
Elizabeth Tarka, M.D., FACC	Director, Cardiovascular & Metabolic MDC
David M. Tenero, Pharm.D.	Director, Clinical Pharmacokinetics
Nevine Zariffa	Therapy Area Director, Cardiovascular and Metabolism Biomedical Data Sciences



Study 902

The sponsor described their proposed protocol entitled, "A Randomized, Double-Blind, Placebo Controlled Study to Compare the β_1 - Blocking Effects of Carvedilol Phosphate MR Capsule Formulation to COREG® Immediate Release Tablets at Two Active Does Levels, at Steady State, in Male and Female Adult Patients with Essential Hypertension, by Evaluating Heart Rate Response to Bicycle Ergometry." During the presentation, the sponsor discussed their objectives and endpoints for their trial, as well as their trial design.

The sponsor proposes a three-parallel-dose-group (placebo, low target dose, and high target dose) trial with 50 patients, 40 on carvedilol and 10 on placebo. The beta-1-adrenergic blocking effect of carvedilol MR and IR that will be assessed through the study of heart rate response to bicycle ergometry will be correlated to PK parameters. A lengthy discussion of the exercise randomization program showed that for the 9-day trial, patients will be randomized to exercise at various intervals on day 7, about 4 times that day. The sponsor informed the Division that they are still working on the randomization scheme. On day 6, blood sample will be taken to assess PK at trough, and on day 8 a full PK profile will be done.

The role of the placebo group was also discussed. The sponsor informed the Division that a placebo group will be used as recommended by the Division in a previous meeting. The sponsor stated that they will not utilize the data from the placebo group for the primary statistical analyses, but wants to collect PK/PD data to see if the placebo changes over time.

The sponsor outlined the primary, secondary, and tertiary endpoints. Dr. Temple recommended that in addition to the AUEC as the primary endpoint, the sponsor should show bioequivalence at trough for the MR formulation.

QUESTIONS

1. Placebo Group

1a. Unbalanced Randomization. Based on discussion at the 24 May 2004 meeting with the FDA, it was agreed that randomization to placebo could proceed in an unbalanced fashion give supportive rationale. Given the sample size estimates, a sufficient number of patients will be randomized to placebo with a target of having 10 patients complete the placebo arm of the study. This number of patients should provide an adequate estimate of any placebo effect over the duration of the study. Therefore the sponsor plans to randomize patients in an unbalanced

fashion to one of the three dose groups (placebo, low target dose, or high target dose) in a ration of 1:2:2. Does the Agency agree with this allocation ratio?

The Division agrees with this allocation ratio.

1b. Use of Placebo Data. Four previous studies evaluating the beta-1- blocking effect of steady-state metoprolol in healthy volunteers have utilized a placebo treatment arm and shown minimal fluctuation of heart rate over time after serial exercise testing. [Lucker, 1990] A study evaluating the beta-1- blocking effect of carvedilol after single dosing in healthy volunteers showed a nonsignificant 2 to 4 beat/min increase in heart rate over time after serial exercise testing in the placebo treatment arm. [de Mey, 1994a; de Mey. 1994b] However, in a recent GSK study (Protocol SK&F-105517/395) evaluating the beta-1-blocking effect of carvedilol in healthy volunteers, a placebo treatment group was not included. In this study, an increase in pharmacodynamic effect was observed at 24 hours postdose in the IR carvedilol 25 mg Q12H X 2 doses group (an approximate 6 beat/min change in heart rate). Therefore, in order to better interpret the data in Study 902, GSK agrees to include a placebo group in the study. Placebo data will not be used in the primary statistical analyses of the pharmacodynamic data, but will be used in the PK/PD analyses. Does the Agency agree with this approach to the use of placebo data?

The Division agrees with this approach to the use of the placebo data. See discussion above.

2. Timing of "Trough" PK/PD

2a. In Study 395, a number of subjects in the 25 mg Q12H dose regimen showed an unexpected increase in beta-1-blockade at the 24-hour timepoint vs. what would have been predicted for the given S(-) carvedilol concentration. The reason for these occurrences are not fully understood, and this led to unexpectedly wide variability for C24. It is theoretically possible that the alterations in administration of meals and snacks during the study day, or the requirement for the subject to remain in the supine position for most of the day may have influenced this result.

2b. By having patients admitted to the clinical research unit on the evening of Day 5 (sessions 3 and 4), the sponsor can be assured of the timing of all study drug administration during Day 6. In addition, the provision of meals and snacks of Day 6, and patient activity, will be identical to that of other pharmacokinetic studies. Pharmacokinetic sampling will occur at each BET timepoint on Day 7 of Sessions 3 and 4. In addition, full pharmacokinetic assessments will be performed on Day 8 in Session 3 and on Days 8 and 9 in Session 4 to evaluate intra-patients variability of IR and MR formulation. Does the Agency agree with this approach?

The Division agrees with this approach.

3. Primary Comparison of Interest.

The AUEC, as a measure of beta-1-blockade over 24 hours will serve as the primary pharmacodynamic endpoint. PDmin, along with PDmax reflections of beta1-blockade at discrete timepoints will be regarded as secondary pharmacodynamic endpoints. Does the Agency agree with this approach?

The Division recommends that the sponsor use the trough effect as the primary endpoint as well as assessing the proposed AUEC.

4. Non-inferiority margin

The primary focus of the statistical analysis is to demonstrate non-inferiority of the beta1-blocking effects of the carvedilol modified-release formulation to COREG immediate-release formulation via comparison of AUEC at steady state between the two formulations. Point estimates and associated 90% confidence intervals will be constructed for the difference MR-IR. Non-inferiority will have been demonstrated if the lower bound of the one-sided 95% confidence interval for the difference MR-IR is no more than 30% of the mean AUEC observed for the IR formulation. Does the Agency agree with this approach?

The Division cannot comment on this approach at this time. It is the sponsor's responsibility to make a case that what they propose is reasonable.

CONCLUSIONS/ RECOMMENDATIONS

The Division recommends that the sponsor consider the discussions and suggestions described above in preparing their phase 3 clinical trials. The sponsor was encouraged to contact the Division if they need additional assistance.

Signature recorder: (see electronic signature below)
Dianne C. Paraoan

Concurrence, Chair: (see electronic signature below)
Robert Temple, M.D.

Draft: 9/1/04 Final: 9/16/04
RD:

Temple: 9/15/04
Stockbridge: 9/14/04
Marciniak: 9/14/04
Karkowsky: 9/13
Lemtouni: 9/13/04
Gobburu: 9/3/04
Velazquez: 9/3/04
Lawrence: 9/3/04

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/s/

Robert Temple
9/16/04 04:48:43 PM

May 24, 2004

Drug: Coreg (carvedilol) Modified Release Formulation
IND: 27,114
Sponsor: GlaxoSmithKline.

Date Requested: May 6, 2004
Date Confirmation Faxed: May 6, 2004
Briefing Package Received: May 7, 2004

Type: Guidance
Classification: C

FDA Participants:

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Acting Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Thomas Marciniak, M.D.	Team Leader, Clinical, HFD-110
Salma Lemtouni, M.D., M.P.H.	Medical Officer, HFD-110
Patrick Marroum, Ph.D.	Team Leader, Biopharmaceutics, HFD-860
Lydia Velazquez, Pharm.D.	Pharmacokineticist and Biopharmaceutist, HFD-860
Jogarao Gobburu, Ph.D.	Team Leader, Pharmacometrics, HFD-860
Melissa Robb	Regulatory Health Project Manager, HFD-110

Sponsor Participants:

Charlotte Baidoo	Senior Statistician, Clinical Pharmacology Statistics and Programming
Catherine K. Clark	Director, US Regulatory Affairs - Cardiovascular
Duane Boyle, Pharm.D.	Director, CVU, Clinical Pharmacokinetics/Modeling & Simulation
Terry L. Holcslaw, Ph.D.	Director, Clinical Research, Cardiovascular/Metabolic Therapeutic Area
Malini Iyengar, Ph.D.	Principal Statistician, Clinical Statistics and Programming
Clare Kahn, Ph.D.	Vice President, US Regulatory Affairs, Cardiovascular, Urogenital, Metabolic
Mary Ann Lukas, M.D.	Senior Director, Medicine Development Center - Cardiovascular
Choon K. Oh, Ph.D.	Director, Pharmaceutical Development
	Consultant, _____

Ruth Ann Subach, Pharm.D., BCPS	Manager, Clinical Pharmacology, Cardiovascular
Elizabeth Tarka, M.D., FACC	Director, Cardiovascular & Metabolic MDC
David M. Tenero, Pharm.D.	Director, Clinical Pharmacokinetics
Nevine Zariffa	Therapy Area Director, Cardiovascular and Metabolism, Biomedical Data Sciences

Background:

Carvedilol is currently approved as an immediate release formulation for the treatment of essential hypertension, mild to severe congestive heart failure and to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of $\leq 40\%$. For all three indications, carvedilol is to be taken twice daily. The sponsor is developing a new formulation that has modified-release (MR) characteristics and would allow for once daily dosing, to be referred to as Coreg-MR. The sponsor has met previously with the Division to discuss the development of a MR formulation on April 30, 2003, August 6, 2003 and November 25, 2003. The sponsor requested this meeting to discuss two protocol outlines (protocols 902 and 369). Protocol 902 is a randomized, double-blind study to correlate pharmacokinetics and pharmacodynamics by comparing the beta-1

adrenergic blocking effect of the modified release formulation to that of Coreg IR tablets at 3 dose steady state levels in male and female adult patients with essential hypertension. The beta blocking effect in both formulations will be assessed using heart rate response to bicycle ergometry. Protocol 369 will be a study in chronic heart failure patients comparing the pharmacokinetics of the two formulations. In addition, the sponsor would like to discuss the analyses resulting from Protocol 395, the initial pilot study for building and developing the PK/PD model for the MR formulation of carvedilol.

Meeting:

The meeting began with the sponsor providing a presentation with the overview of their development program for Coreg MR. The sponsor stated they did not plan to discuss the development of Coreg MR in hypertension at this meeting, as this had already been agreed upon with the Division in previous meetings. However, a brief overview of the study planned for the development in this indication was presented. The study planned is a double-blind, placebo-controlled trial looking at the 20, 40 and 80 mg doses of Coreg MR vs. placebo. Other aspects of the development program, specifically, the PK and PD of Coreg MR, the sponsor planned on discussing during this meeting.

The sponsor then presented figures illustrating the plasma concentrations of carvedilol vs time on the IR formulations and 2 potential MR formulations. The Division noted that with the IR formulation, the second dose in a 24 hour period produces a lower peak. The sponsor believes this is related to a diurnal effect and a slowed GI motility in the evening. The sponsor stated this occurs at steady state and there is a 25% accumulation in the IR formulation. The Division stated that they would want data provided to illustrate how the plasma concentrations are effected by AM versus PM dosing with the MR formulation. The sponsor inquired if a single dose administration would be sufficient to characterize AM vs PM administration. The Division believed this would be acceptable as long as the sponsor felt they would be able to model the diurnal effect at steady state.

The Division also expressed some concern with the variability shown in the figures illustrating individual patient plasma concentrations of carvedilol in the MR formulations. The Division believed it will be important for the sponsor to show reproducibility in the daily dosing. The sponsor stated that there was also great variability noted in individual patients' plasma concentrations with the IR formulation currently marketed. The sponsor stated their goal with this development program is to link beta blockade to serum concentrations. The Division was concerned with the variability in an indication such as heart failure, where dose is titrated based on tolerance and not effect, and there is no outcome data to support an approval. The sponsor inquired if it would be acceptable to show that the variability seen in the MR formulation was similar to that which is seen in the IR formulation. The Division agreed, but stated they would be taking into consideration any extremes noted. The sponsor added that there are 2 IR formulations which have different PK profiles currently being marketed, one in the EU and one in the US, both of which have a documented mortality benefit. The Division also noted that the figures showed lower peaks in the MR formulation. The sponsor acknowledged this fact, but stated the 2 formulations are very comparable. The Division noted their concern that they did not want to approve a new formulation which does not provide the benefits seen in the currently approved formulation. The Division noted that in the past they had agreed that if the sponsor were able to match peak, trough and AUC that would be acceptable for approval.

The sponsor then provided an overview of their planned study 902 in which they plan to compare the beta blocking effects of Coreg MR and IR at three doses in patients with essential hypertension.

Study 902 Questions:

1. The sponsor has concluded that sufficient data (*Br J Clin Pharmacol* 1994,38:480-483; *J Clin Pharmacol* 1990,30:S17-S27; *Clin Pharmacol Ther* 1994,55:329-337) are available to support that no placebo effect is seen when bicycle ergometry is used to evaluate β_1 -blockade; therefore, the sponsor is proposing to not include a placebo group. Does FDA agree?

The Division stated they did not like the idea of the trial without a placebo group. After reviewing the articles referred to by the sponsor, the Division believes it would be hard to judge the absolute magnitude of the beta blockade effect. The Division stressed the importance of a placebo arm especially that the observed diurnal effect is neither qualified or quantified and that there is a potential for a training effect that might interact with the difference (continuous vs. bimodal) in beta blockade between the two formulations. The Division was unsure how the sponsor would be able to tease out these effects without a placebo in order to create a model. The sponsor felt this was not important since the placebo effect would be subtracted out from both groups. The Division expressed another concern that without a placebo group, the Division would be unable to tell how much of a difference matters when comparing the IR and MR formulations. The Division encouraged the sponsor to make a case for the Division to review if they believe no placebo group is needed in the trial. (Note: baseline ergometry at the same time points as efficacy measurements are important. Since the metric of interest is % beta blockade versus drug concentrations, if there is diurnal variation in the increase in exercise heart rate, the beta blockade effect cannot be assessed without 24-hour measurements.)

2. The current concept protocol has been written to include the labeled IR doses for treatment of hypertension (6.25 mg q12 h, 12.5 mg q12 h, 25 mg q12 h). The vast majority of patients with CHF are also treated with these three dose levels as the starting dose of 3.125 mg q12 h is primarily used to assess initial tolerability to beta blocker therapy. Due to feasibility concerns, the sponsor proposes that only the low and the high dose levels (6.25 mg q 12 h vs MR 20 mg qd; 25 mg q12 h vs MR 80 mg qd) need to be investigated in this protocol as they bracket the range of doses used in most patients. If similarity of the PD effect is demonstrated between the IR and MR formulations for the low and high dose groups, it is assumed that PD similarity exists between the IR and MR formulations for the middle dose group (12.5 mg q12 h vs MR 40 mg qd). To support this proposal, the sponsor will conduct simulations which will be discussed with the FDA prior to finalization of the protocol. Does the FDA agree with this approach?

The Division believes this approach is acceptable for this study for PK/PD correlation. However, this approach would not be acceptable in another setting where biopharmaceutical issues were in question and the formulation is not compositionally proportional throughout all strengths. Since we have no information regarding contents of the formulation the Division wanted to clarify that this is the only setting where this is appropriate at this time.

The Division also commented that another PD collection time period is necessary between 1.5 and 6 hours.

The sponsor then provided an overview of their planned study 369 which will compare the PK characteristics of the MR and IR formulations. The sponsor stated the study design for this protocol has changed since first discussed with the Agency in April 2003.

Study 369 Questions:

1. Is the FDA in agreement with the use of an open label, nonrandomized crossover design for this study?

The Division agreed.

2. Does the FDA view having uptitration safety information for Coreg MR as necessary? If so, does the FDA view the amount of uptitration safety information for the MR formulation to be adequate?

The sponsor added that there will be data available from approximately 400 patients in the hypertension trial. Titration will occur for patients with this indication as tolerated. The Division agreed that uptitration safety information would not be required.

3. It is anticipated that patients receiving 3.125 mg bid may be underrepresented. In particular, enrollment of recent survivors of an acute MI with LVD will be difficult since current labeling instructs patients be initiated at 6.25 mg bid. Also, use of 3.125 mg bid for heart failure patients is more for treatment initiation than specific

therapeutic effects. Does the FDA view potentially having sparse PK data at this dose of Coreg IR and MR as a significant issue?

The Division inquired about the number of heart failure patients on the 3.125 mg dose. The sponsor was unsure of the exact numbers. The sponsor plans to have all doses represented, but is unsure if some of the doses will only have PK data from a small number of subjects. The Division did not believe this should be a significant issue. The Division inquired how the sponsor plans to handle any missing data. The sponsor was unsure at this time, but thought they would possibly try to extrapolate it.

The Division also noted some concern with PK data collected, since the sponsor stated earlier that there are differences in PK noted in patients with heart failure.

The sponsor inquired about how the results of food effect trials are handled. The Division stated that the results are to be descriptive in nature, and used to see if dose dumping occurs in the new formulation and also for labeling. The Division added that it would be problematic if dose dumping was seen when using the standard FDA meals.

The Division also addressed the sponsor's request for concurrence from the Agency that the program described requires no additional studies and is adequate to support approval. The Division stated that is hard to answer since the sponsor has not yet decided on a final formulation they plan to market. There may be biopharmaceutical issues that will require the sponsor's attention prior to NDA submission. The sponsor acknowledged that fact and inquired specifically about clinical development. The Division agreed that the clinical development program seems adequate to support approval.

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The Division noted the need for a pediatric development plan for this formulation. The Division was unsure if it would be waived for this formulation. However, the Division added it is likely the Division will waive the requirement for products where it is believed that data will be coming in. The Division concluded by stating it would be reasonable to assume that the pediatric requirement would be either waived or deferred at the time of submission.

Signature, minutes preparer: _____

Concurrence Chair: _____

Drafted: 5/26/04

Finalized: 6/2/04

RD:

Stockbridge	6/1/04
Karkowsky	6/1/04
Marciniak	5/28/04
Lemtouni	5/27/04
Marroum	5/26/04
Gobburu	5/26/04
Velazquez	5/26/04

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this page is the manifestation of the electronic signature.**

/s/

Melissa Robb
6/2/04 08:12:11 AM

Norman Stockbridge
6/2/04 11:03:49 AM

Minutes of a Meeting
April 30, 2003

Drug: Coreg (carvedilol) Modified Release Formulation

Sponsor: GlaxoSmithKline.

Date Originally Requested: July 25, 2002
Date of Last Reschedule Request by GSK: March 11, 2003
Date Confirmation Faxed: March 12, 2003
Briefing Package Received: April 17, 2003

Type: Guidance
Classification: C

FDA Participants:

Robert Temple, M.D.	Director, ODE I, HFD-101
Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Mehul Desai, M.D.	Medical Officer, HFD-110
Salma Lemtouni, M.D.	Medical Officer, HFD-110
Albert DeFelice, Ph.D.	Team Leader, Pharmacology, HFD-110
James Hung, Ph.D.	Team Leader, Statistics, HFD-710
Charles Le, Ph.D.	Statistician, HFD-710
Valeria Freidlin, Ph.D.	Statistician, HFD-710
Jogarao Gobburu, Ph.D.	Pharmacometrics, HFD-860
Lydia Velazquez, Pharm.D.	Pharmacokineticist and Biopharmaceutist, HFD-860
Melissa Robb	Regulatory Health Project Manager, HFD-110

Sponsor Participants:

Catherine K. Clark	Director, NA Regulatory Affairs
Clare Kahn, Ph.D.	Vice President, Regulatory Affairs, Cardiovascular, Urogenital and Metabolism
Duane Boyle, Pharm.D.	Director, Clinical Pharmacokinetics
Terry Holcslaw, Ph.D.	Director, Clinical Development, Cardiovascular Therapeutic Area
Malini Iyengar	Principal Statistician, New Product Development
Mary Ann Lukas, M.D.	Senior Director, Cardiovascular Therapeutic Area, NA Medical Affairs
Rosemary Oakes	Associate Director, Statistics & Programming, Biomedical Data Sciences
Steve Okada, M.D.	Director, Clinical Development/Medical Affairs
Ruth Ann Subach, Pharm.D., BCPS	Clinical Pharmacology & Discovery Medicine, Full Development Manager
David Tenero, Pharm..D.	Clinical Pharmacology, Cardiovascular & Urogenital Diseases Manager, Pharmacokinetics Section, New Product Development Consultant,

Background:

Carvedilol is currently approved as an immediate release formulation for the treatment of essential hypertension, mild to severe congestive heart failure and to reduce cardiovascular mortality in clinically stable patients who have survived the

acute phase of a myocardial infarction and have a left ventricular ejection fraction of $\leq 40\%$. For all three indications, carvedilol is to be taken twice daily. The sponsor is developing a new formulation that has modified-release characteristics and would allow for once daily dosing, to be referred to as Coreg-MR. The sponsor has not yet identified a formulation that will be developed commercially. Once this formulation is identified, they plan to schedule a separate meeting to discuss Chemistry, Manufacturing and Controls and Clinical Pharmacology and Biopharmaceutics issues for the proposed modified release formulation.

Meeting:

Dr. Temple began by inquiring as to whether or not the sponsor has decided on a formulation that they plan to use in the proposed trials and for marketing. He expressed concern with Figure 1 presented in the Briefing Document which depicted the time course of plasma levels for one of the candidate Modified Release (MR) formulations as compared with the approved Immediate Release (IR) formulation. He pointed out that the plasma levels are not sustained over the latter portion of the dosing period (half a day) for the MR formulation. The sponsor stated they are primarily looking at two different formulations. They are hoping to get a formulation with better time course plasma levels. They have not yet done food effect studies or repeat dose studies on both formulations, but they believe the blood levels will improve with the additive effect of the drug. The sponsor stated that the other formulation they are considering also goes below C_{min} during the 24 hour period with values of —. The sponsor stated they have had great difficulty in finding a suitable MR formulation and have tried over — formulations. The primary difficulty they have had with developing this MR formulation is decreased bioavailability of the drug as it proceeds through the GI tract. As a result, the sponsor does not believe that the total daily IR dose will equal the MR dose. The MR dose will probably have to be higher in order to achieve the same plasma concentrations and exposure. The Agency agreed that historically there has been a preference for new formulations of a drug not to have a lower bioavailability, but this preference can be overcome if there is a good reason, such as a decrease in dosing frequency. Thus, the Agency believes that the dose of the MR formulation taken once daily does not need to be equal to that of the IR formulation taken twice daily. The Agency and sponsor agreed that this would require prescribers to be educated on correct dosing of the two different formulations. The Agency advised the sponsor to research how this situation was handled with the approval of Clonidine patches.

The Agency believes the proposed force titration trial for the development of the MR formulation in patients with hypertension was acceptable, but suggested the sponsor consider using a parallel dose design. The Agency believes the potential advantages of a parallel group design would include having less difficulty handling dropouts and that it would better allow for the collection of data to describe blood pressure effect related to dose. On the other hand, the Agency believes that if the sponsor is confident that they know that a pharmacodynamic steady state is achieved relatively early, then their proposed study design would provide the dose-effect information needed for labeling. The sponsor believes that in original studies of carvedilol, steady-state was achieved at one week, with no changes noted between one week and two weeks. The sponsor acknowledged that a longer period of time between increasing doses would allow for greater assurance that steady-state was achieved. The Agency agreed with this fact also, but is concerned about having patients in the placebo group off treatment for longer than the proposed 10 weeks. The Agency also suggested including an IR twice daily Carvedilol arm in order to compare with the effects of the MR formulation (The total daily IR dose should be equal to the modified release dose). The Agency acknowledged there would be a risk in including an IR arm, as the MR formulation may show a decreased effect compared to the IR formulation. The Agency also suggested including an arm of the MR formulation taken twice daily, as they believe the MR might be a better BID formulation than the IR form currently being marketed. The Agency also pointed out that with the proposed number of patients in the study, any drop-outs could be very detrimental to the results.

The Agency believes that for the development of the MR formulation for heart failure it is important to understand the relationship between plasma concentrations of carvedilol and effect as measured by beta blockade (reduction in exercise induced tachycardia) along with the concentrations achieved with the two formulations. With this understanding, the Agency would be able to look at the pharmacokinetic profile of the MR formulation of the drug and determine whether patients would be below the threshold of the beta blockade effect and the duration they are under this threshold over 24

hours. The Agency believes that a study to assess the PK/PD effects of the drug with several doses could be done in healthy patients, as they are a more sensitive population to the measures of beta blockade. The Agency did not require this data in the approval of the IR formulation because the sponsor collected clinical data that was able to show that the drug was effective. Although the sponsor has proposed 24 hour Holter monitoring to be collected during the trial, the Agency believes resting heart rate is not a good measure of beta blockade. The Agency suggested the sponsor evaluate the program used for the approval of Inderal LA as a reference. The Agency is relying on the assumption that too much beta blockade is better than not enough and that the MR formulation would need to show equal or greater time of beta blockade over 24 hours compared to the IR formulation dosed twice daily. The Agency believes a trial using multiple doses would be best, but also agreed that study of an optimum dose could also be acceptable. The Agency encouraged the sponsor to look at the approval of labetalol as they showed an effect on heart rate related to plasma concentrations. The Agency believes this study, in addition to the proposed study to gain pharmacokinetic data in patients with heart failure, would allow for a link between the IR and MR formulations. The Agency encouraged the sponsor to interact with the clinical pharmacology reviewers regarding the specifics of the design of these studies.

Signature, minutes preparer: _____

Concurrence Chair: _____

Drafted: 4/30/03 Finaled: 5/12/03

RD:

Temple	5/9/03
Throckmorton	5/8/03
Stockbridge	5/8/03
Desai	5/2/03
Lemtouni	5/4/03
DeFelice	5/6/03
Hung	5/6/03
Le	5/5/03
Freidlin	5/6/03
Gobburu	5/8/03
Velazquez	5/7/03

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/s/

Melissa Robb

1/20/04 09:02:43 AM

Signed by Dr. Temple and faxed to sponsor 5/12/03

Teleconference Minutes
November 25, 2003

IND# 27,114
Drug: Coreg (carvedilol) Tablets
Sponsor: GlaxoSmithKline

Date Requested: October 16, 2003
Date Confirmation Faxed: October 17, 2003
Briefing package received: October 16, 2003
Updated Briefing package received: November 21, 2003, via e-mail

Type: Biopharm/Bioequivalence
Classification: C

FDA Participants:

Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Patrick Marroum, Ph.D.	Team Leader, Biopharmaceutics, HFD-860
Mehul Desai, M.D.	Medical Officer, HFD-110
Russell Fortney	Regulatory Health Project Manager, HFD-110

GlaxoSmithKline Participants:

Duane Boyle, Pharm.D.	Director, Cardiovascular and Urogenital-VU ₇ , Clinical Pharmacokinetics/Modeling & Simulation
Catherine K. Clark	Director, NA Regulatory Affairs
Michael Fossler, Ph.D.	Principal Clinical Pharmacokineticist, Clinical Pharmacokinetics
Ruth Ann Subach, Pharm.D., BCPS	Clinical Pharmacology & Discovery Medicine, Full Development Manager, Clinical Pharmacology, Cardiovascular & Urogenital Diseases
David Tenero, Pharm.D.	Manager, Pharmacokinetics Section, New Product Development

Background:

Carvedilol is currently approved as an immediate release formulation for the treatment of essential hypertension, mild to severe congestive heart failure and to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of $\leq 40\%$. For all three indications, carvedilol is to be taken twice daily. The sponsor is developing a new formulation that has modified-release characteristics and would allow for once daily dosing, to be referred to as Coreg-MR. The sponsor met with the Agency to discuss this development program in April 2003 and updated the Agency on the progress made in August 2003. The sponsor has requested this meeting to discuss the protocol summary and data analysis plan for a study entitled, "A Study to Assess the Pharmacokinetic and Pharmacodynamic Relationship of Oral Administration of Immediate- and Modified Release- Formulations of Carvedilol in Healthy Subjects".

Teleconference:

The sponsor began the meeting with a brief overview of the protocol.

Dr. Throckmorton asked the sponsor for clarification of the blinding of the trial. The sponsor explained that only the patients will be blinded. Because of safety concerns, they have chosen to titrate, rather than randomly assign dose levels. The evaluators will be instructed not to encourage subjects to increase their exercise output. Dr. Throckmorton expressed some concern that since because no placebo is given at 12 hours, the blinding could be

affected. He said the sponsor will need to be sure the blinding issue does not affect outcomes. The sponsor agreed to address this issue prior to initiating the trial. Later in the meeting, when the intent of the current trial was clarified, Dr. Throckmorton realized that this trial is intended to be more of a pilot trial, he said that his concerns regarding blinding might not be as important.

Dr. Throckmorton asked if the sponsor has data from other trials comparing carvedilol to placebo. The sponsor said they do, and that no placebo effect was seen in those trials.

Dr. Throckmorton said that one way to detect assay sensitivity in the absence of a placebo would be to demonstrate a dose-related effect from the three IR doses.

Dr. Throckmorton asked how the sponsor intends to claim a win in this trial. The sponsor said that if the results show a PK/PD similarity between the IR and MR doses, they intend to perform another trial comparing the two dosage forms head-to-head.

Dr. Throckmorton asked if carvedilol accumulates with multiple doses. The sponsor said there is about 30% accumulation with multiple doses. Dr. Throckmorton asked if the beta-blockade effects are saturable. The sponsor said that this is seen at high doses. Dr. Throckmorton explained that if the PD curves for the two dosage forms differ, that could potentially be a problem. The sponsor replied that they think that while the MR dosage form will not have the two peaks that the IR form will have, they AUC for the two dosage forms should be similar. In addition, they said that they expect CHF patients to have higher drug levels with flatter curves.

The sponsor asked if a single dose level is acceptable for the hypertension trial. Dr. Marroum suggested that they should study a lower dose as well. The sponsor asked if they should work through the data with the Division. Dr. Throckmorton said that it would be a good idea to do that.

Regarding the sponsor's desire to label and express the dose of the MR product as the _____ in the labeling, Dr. Throckmorton said that is acceptable.

Signature, minutes preparer: _____

Concurrence, Chair: _____

Drafted: 11/26/03 Finaled: 12/1/03

RD:

Throckmorton 12/1/03
Stockbridge 12/1/03
Marroum 12/1/03
Desai 12/1/03

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

/s/

Russell Fortney
12/1/03 01:55:29 PM

Doug Throckmorton
12/3/03 08:10:20 AM

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Draft Labeling

Deliberative Process