

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-700

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

21-700

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)

Avandaryl

ACTIVE INGREDIENT(S)

Rosiglitazone maleate
Glimepiride

STRENGTH(S)

4 mg Rosiglitazone maleate/4 mg Glimepiride
4 mg Rosiglitazone maleate/2 mg Glimepiride
4 mg Rosiglitazone maleate/1 mg Glimepiride

DOSAGE FORM

Tablet

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.

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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

4,379,785

b. Issue Date of Patent

4/12/1983

c. Expiration Date of Patent

4/6/2005

d. Name of Patent Owner

Hoechst AG

Address (of Patent Owner)

Hoechst Aktiengesellschaft
Industriepark Höchst

City/State

65926 Frankfurt am Main

ZIP Code

Germany

FAX Number (if available)

+4969 357175

Telephone Number

+4969 305 12104

E-Mail Address (if available)

steffen.rupp@aventis.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)

 Ross Oehler, Esq.

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

Aventis Pharmaceuticals Inc.
Route 202-206
P.O. Box No. 6800

City/State

Bridgewater, NJ

ZIP Code

08807-0800

FAX Number (if available)

(908) 231-5730

Telephone Number

(908) 231-2972

E-Mail Address (if available)

ross.oehler@aventis.com

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

Drug Product (Composition/Formulation)

- 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) 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? 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.)
To improve glycemic control in patients with type 2 diabetes mellitus

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 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

Linda Rebar

Aug 10 2004

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

Linda Rebar

Address

GlaxoSmithKline
One Franklin Plaza
200 N. 16th Street

City/State

King of Prussia, PA

ZIP Code

19102

Telephone Number

(215) 751-4038

FAX Number (if available)

E-Mail Address (if available)

linda.rebar@gsk.com

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

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**PATENT INFORMATION SUBMITTED WITH THE
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*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
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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, please refer to section 5 and 6.

1. GENERAL

a. United States Patent Number

5,002,953

b. Issue Date of Patent

3/26/1991

c. Expiration Date of Patent

8/30/2008

d. Name of Patent Owner

SmithKline Beecham Corporation

Address (of Patent Owner)

One Franklin Plaza
P.O. Box 7929

City/State

Philadelphia, PA

ZIP Code

19101-7929

FAX Number (if available)

Telephone Number

(215) 751-4000

E-Mail Address (if available)

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.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

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

Drug Product (Composition/Formulation)

- 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) 53 (Additional claim(s) listed in Attachment) 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.)
To improve glycemic control in patients with type 2 diabetes mellitus

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 manufacture, use, or sale of the drug product. Yes

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Date Signed

Linda Rebar

Aug 10 2004

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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

Linda Rebar

Address

GlaxoSmithKline
One Franklin Plaza
200 N. 16th Street

City/State

Philadelphia, PA

ZIP Code

19102

Telephone Number

(215) 751-4038

FAX Number (if available)

E-Mail Address (if available)

linda.rebar@gsk.com

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1. GENERAL

a. United States Patent Number

5,741,803

b. Issue Date of Patent

4/21/1998

c. Expiration Date of Patent

4/21/2015

d. Name of Patent Owner

SmithKline Beecham plc

Address (of Patent Owner)

980 Great West Road

City/State

Brentford, Middlesex TW8 9GS

ZIP Code

United Kingdom

FAX Number (if available)

+44 020 8047 6894

Telephone Number

+44 020 8047 5000

E-Mail Address (if available)

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)

 Charles M. Kinzig, Esq.

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

GlaxoSmithKline
709 Swedeland Road

City/State

King of Prussia, PA

ZIP Code

19406-0939

FAX Number (if available)

(610) 270-5090

Telephone Number

(610) 270-5021

E-Mail Address (if available)

charles.m.kinzig@gsk.com

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

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- 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
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Drug Product (Composition/Formulation)

- 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
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- 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) 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? Yes No
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Date Signed

Linda Rebar

Aug 10 2004

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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

Linda Rebar

Address

GlaxoSmithKline
One Franklin Plaza
200 N. 16th Street

City/State

Philadelphia, PA

ZIP Code

19102

Telephone Number

(215) 751-4038

FAX Number (if available)

E-Mail Address (if available)

linda.rebar@gsk.com

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1. GENERAL

a. United States Patent Number

6,288,095

b. Issue Date of Patent

9/11/2001

c. Expiration Date of Patent

2/11/2017

d. Name of Patent Owner

Beecham Group plc

Address (of Patent Owner)

980 Great West Road

City/State

Brentford, Middlesex TW8 9GS

ZIP Code

United Kingdom

FAX Number (if available)

Telephone Number

+44 020 8047 5000

E-Mail Address (if available)

+44 020 8047 6894

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)

 Charles M. Kinzig, Esq.

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

GlaxoSmithKline
709 Swedeland Road

City/State

King of Prussia, PA

ZIP Code

19406-0939

FAX Number (if available)

(610) 270-5090

Telephone Number

(610) 270-5021

E-Mail Address (if available)

charles.m.kinzig@gsk.com

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

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- 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

Drug Product (Composition/Formulation)

- 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) 1 (Additional claim(s) listed in Attachment) 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.)
To improve glycemic control in patients with type 2 diabetes mellitus

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 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

Linda Rebar

Aug 10 2004

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

Linda Rebar

Address

GlaxoSmithKline
One Franklin Plaza
200 N. 16th Street

City/State

Philadelphia, PA

ZIP Code

19102

Telephone Number

(215) 751-4038

FAX Number (if available)

E-Mail Address (if available)

linda.rebar@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.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-700 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: September 26, 2005 (second review cycle) PDUFA Goal Date: November 26, 2005

HFD-510 Trade and generic names/dosage form: Avandaryl (rosiglitazone maleate and glimepiride) Tablets

Applicant: SB Pharmco Puerto Rico Inc. d/b/a GlaxoSmithKline Therapeutic Class: antidiabetic agent

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 question.
- 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): N/A

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

Number of indications for this application(s): One

Indication #1: Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of rosiglitazone and sulfonylurea or who are not adequately controlled on a sulfonylurea alone or for those patients who have initially responded to rosiglitazone alone and require additional glycemic control.

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.

NDA 21-700

Page 3

This page was completed by:

{See appended electronic signature page}

**Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)

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/s/

Lina Aljuburi

1/25/2007 12:41:37 PM

Approval letter issued November 23, 2005, waiving pediatric studies.
To date, pediatric page had not been entered
into DFS.

NDA 21-700 Avandaryl
(rosiglitazone maleate/glimepiride) Combination Tablets

New Drug Application for:
Treatment of Type 2 Diabetes Mellitus

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
Director, North America Clinical Compliance
Worldwide Regulatory Compliance

Date

Aljuburi, Lina

From: Aljuburi, Lina
Sent: Friday, November 25, 2005 12:17 PM
To: CDER-APPROVALS
Subject: NDA 21-700 Avandaryl Tablets APPROVAL on November 23, 2005

Good afternoon,

NDA APPROVAL

Date of Approval: **November 23, 2005**
NDA #: **21-700**
Name of drug: **Avandaryl Tablets (rosiglitazone maleate and glimepiride)**
Name of Sponsor: **SB Pharmco Puerto Rico Inc. d/b/a GlaxoSmithKline**
Indication: **as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of rosiglitazone and sulfonyleurea or who are not adequately controlled on a sulfonyleurea alone or for those patients who have initially responded to rosiglitazone alone and require additional glycemic control**
Dosage form/route of administration: **Tablet/Oral**
Is this dosage form/route of administration new?: **Yes**
Rx, OTC or Rx to OTC switch: **Rx**
Drug classification and review priority rating: **4S**

Feel free to contact me if you have any questions regarding this NDA approval.

Many thanks,
Lina

*Lina Aljuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-1168 (phone)
301-796-9712 (fax)*

Aljuburi, Lina

From: Margaret.M.Kreider@gsk.com
Sent: Wednesday, November 23, 2005 1:15 PM
To: Aljuburi, Lina
Subject: Re: FW: NDA 21-700 Avandaryl Approval Letter with Labeling

Lina,

I received your email with the action letter.

Thank you and have a Happy Thanksgiving!

Marge

Margaret Kreider
GlaxoSmithKline
US Regulatory Affairs

"Aljuburi, Lina" <ALJUBURIL@cder.fda.gov>

23-Nov-2005 13:09

To "Margaret.M.Kreider@gsk.com" <Margaret.M.Kreider@gsk.com>
cc
Subject FW: NDA 21-700 Avandaryl Approval Letter with Labeling

Hi, Marge

The action letter for NDA 21-700 Avandaryl (rosiglitazone maleate and glimepiride) Tablets has just issued. I am attaching it to this email for your reference. Please send me an email confirmation when you receive this email. Feel free to contact me if you have any questions.

<<AP_LetterToSpon_11.23.05.pdf>>

Happy Thanksgiving!

Lina

Lina Aljuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration

301-796-1168 (phone)

301-796-9712 (fax) [attachment "AP_LetterToSpon_11.23.05.pdf" deleted by Margaret M

11/23/2005

Kreider/PharmRD/GSK]

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Aljuburi, Lina

From: Duffy, Felicia
Sent: Tuesday, November 22, 2005 1:57 PM
To: Aljuburi, Lina
Subject: RE: NDA 21-700 revised container labels

Hi Lina,

This is in response to GSK's revised labeling revisions for Avandaryl from the DMETS review dated November 17, 2005 (ODS consult 04-0051-2).

DMETS notes the magenta (4 mg/1 mg) and green (4 mg/2 mg) color of the Avandaryl product strength correlates to the 1 mg and 2 mg strengths of Amaryl, respectively. Although the colors are similar, we acknowledge the significant difference in the presentation of the Avandaryl and Amaryl container labels. Thus we have no further comments on the revised Avandaryl labels.

Thanks,

Felicia

Felicia Duffy, RN, BSN
LCDR USPHS
Safety Evaluator, DMETS
Office of Drug Safety, FDA
White Oak, Bldg.22, Rm. 4417
Phone: 301-796-0148
Fax: 301-796-9865

-----Original Message-----

From: Aljuburi, Lina
Sent: Monday, November 21, 2005 4:48 PM
To: Duffy, Felicia
Subject: FW: NDA 21-700 revised container labels

Hi, Felicia

GSK has responded to the recommendations and suggestions from your review dated November 17, 2005, for NDA 21-700 Avandaryl Tabs.

Would you mind taking a look at the comments in the email below and the attachment?

We are trying very hard to take an action Tuesday, November 22nd.

I know you must be swamped.

Let me know if you have any questions.

Thank you so much for all your help!

Lina

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager

Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-1168 (phone)
301-796-9712 (fax)

-----Original Message-----

From: Margaret.M.Kreider@gsk.com [mailto:Margaret.M.Kreider@gsk.com]
Sent: Monday, November 21, 2005 4:29 PM
To: Aljuburi, Lina
Subject: NDA 21-700 revised container labels

Lina,

Please find attached revised container labels for Avandaryl. We have provided the label for the 4 mg/2 mg tablet strength in the attached pdf file.

In addition, the colors for the 4 mg/1 mg and the 4 mg/4 mg tablet strengths are shown at the bottom of the page. The colors are as follows: 4mg/1mg Process Magenta

4mg/2mg PMS 354 green

4mg/4mg PMS 2603 purple

Here are our responses to the comments provided on November 18th.

General Comments

1
ti

2 - We have also used a font for Avandaryl that is different from the fonts for Avandamet, Avandia and Amaryl.

3- We have revised the presentation of the dosage strengths according to option c.

4- We have provided a uniform background color for the strengths

5- Neither yellow nor light blue was used as a color to differentiate the strengths

Container Label Comments

1 - Professional sample and Commercial product

b - the prominence of the proprietary name has been increased

c- the established name prominence has been increased to at least 1/2 the size of the proprietary name

d - the product strength has been relocated to appear in conjunction with the established name

e - the "once daily" has been retained on the sample and on the commercial labels

f - the inverted red triangle has been removed from the letter "v" in Avandaryl

g - the prominence of the net quantity has been decreased

h - both the professional sample bottle and the commercial bottles have child-resistant caps

Please call me if you need additional information.

11/23/2005

Regards,

Marge

Margaret Kreider
GlaxoSmithKline
US Regulatory Affairs

Appears This Way
On Original

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On Original

11/23/2005

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: Novemeber 17, 2005

FROM: David G. Orloff, M.D.
Director, Division of Metabolism and Endocrinology Products

TO: NDA 21-700
Avandaryl (rosiglitazone maleate and glimepiride) tablets
GlaxoSmithKline
Treatment of type 2 diabetes

SUBJECT: NDA review issues and recommended action

Summary of issues

CMC/compliance

At the end of the first review cycle, there were pending deficiencies based on a Withhold recommendation from OC. These have been addressed to the satisfaction of the ONDC review team, which now recommends approval.

Tradename

Additionally, DMETS recommended against acceptance of the tradename Amaryl due to possible sound-alike, look-alike confusion with Avandia, Amaryl, and Avandamet. The comments were sent to the sponsor. The sponsor responded in a submission dated September 15, 2004, and argues for maintaining the proposed tradename in the setting of risk management around using the correct product, correct doses, and necessity to take Avandaryl with food. I accept their arguments and proposals, as detailed below.

While devising a new tradename for the Avandia-Amaryl combination might obviate medication errors involving substitution, it may instead engender errors resulting in double-dosing, since all the products of concern are indicated for the same population and condition. Double-dosing with Avandia or Amaryl is certainly undesirable, the first risking fluid retention or drug toxicity, the second instance risk hypoglycemia.

On the other hand, if the Avandaryl tradename is retained, there is certainly a risk of errors related to substitution, and the consequences of such events are examined in what follows. First, if Avandaryl is substituted for Avandia or Avandamet, there is a risk of hypoglycemia, though small in the majority of patients (who unfortunately are not well controlled). By contrast, the risk of hypoglycemia with double-dosing of the sulfonylurea component is likely more substantial. Second, if Avandaryl is substituted for Amaryl, there are virtually no additional risks of hypoglycemia. Third, if Avandia, or Avandamet, or Amaryl are dispensed instead of Avandaryl, the patient experiences no risk.

In addition, it must be recognized that the dosage strengths of the different drugs are different. Specifically, as fixed combinations, Avandaryl and Avandamet dosage designations include 2 numbers, one denoting the Avandia dose, the other the Amaryl and metformin doses, respectively. These are distinguishing features that work to reduce the risk of medication errors involving substitution.

The sponsor also proposes communication and education plans for the launch of Avandaryl to emphasize the distinction from Avandamet and the products containing the individual components (Avandia, Amaryl). This is acceptable.

Labeling

Summary

The manufacturing issues have been addressed. The sponsor's proposals and rationale for use of the tradename Avandaryl as opposed to a name that does not convey something about the components of the combination are acceptable. Specifically, the risks associated with double dosing of Avandia or Amaryl, as are more likely with a tradename non-reminiscent of the component drugs, are greater than the risks associated with substitution of Avandaryl for either Amaryl, Avandia, or Avandamet, and vice versa.

The sponsor's proposed additional language in Indications and Usage is acceptable.

Recommendation

Approve. The tradename Avandaryl is acceptable, with risk management as proposed and modification of the label to emphasize the distinction from Avandia, Amaryl, Avandamet.

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/s/

David Orloff
11/21/2005 05:42:07 PM
MEDICAL OFFICER

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; WO22; Mail Stop 4447
Center for Drug Evaluation and Research

PROJECT #: 04-0051-2

DATE OF REVIEW: November 9, 2005

TO: David Orloff, MD
Director, Division of Metabolism and Endocrinology Products
(HFD-510)

FROM: Felicia Duffy, RN
Safety Evaluator, Division of Medication Errors and Technical Support (HFD-420)

THROUGH: Alina Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support (HFD-420)

SUBJECT: **DMETS LABELING REVIEW**
Drug: Avandaryl™
(Rosiglitazone maleate and Glimepiride) Tablets
4 mg/1 mg, 4 mg/2 mg, 4 mg/4 mg
NDA #: 21-700
Sponsor: GlaxoSmithKline

This memorandum is in response to your November 7, 2005 request for review of the revised container labeling for Avandaryl. The sponsor indicated in an email dated November 4, 2005, _____ the 30 count bottles for the three tablet strengths of Avandaryl will be used: 4 mg/1 mg, 4 mg/2 mg, and 4 mg/4.

DMETS previously reviewed the proprietary name Avandaryl in ODS consult 04-0051 dated April 8, 2004. We did not recommend the use of the proprietary name Avandaryl, based on concerns related to look-alike and/or sound-alike confusion with Amaryl, Avandia, and Avandamet. DMETS is currently conducting a post-marketing review of medication errors involving Avandia/Amaryl and Avandia/Avandamet. A preliminary assessment of the root cause of these errors appears to be the similarity in names and the overlapping indication for use, strengths, and dosage form. We will forward this review to the Division upon its completion. Due to these post-marketing errors we anticipate similar post-marketing confusion with Avandaryl. Despite our concerns with the proprietary name Avandaryl, DMETS was informed that the Division decided to approve the Avandaryl tradename \ _____ DMETS does not believe this type of physical differentiation of the name on the labels and labeling will prevent confusion between Avandaryl and Avandia, Amaryl and Avandamet (see comment A-1 on page 2). Thus, we maintain our concern for potential confusion and medication errors with the proposed proprietary name, Avandaryl.

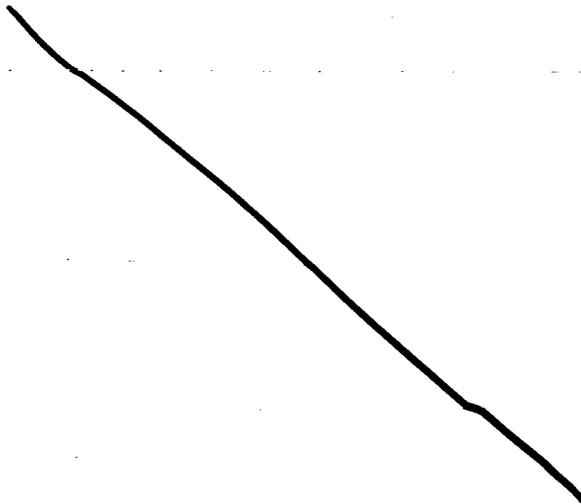
Additionally, since the April 8, 2004 review, DMETS has identified one additional proprietary name, Benadryl, as having look-alike similarities to Avandaryl. Benadryl is available over-the-counter (tablets, capsules, oral solution, and cream) and as a prescription (injection). Since Avandaryl is administered orally, and the route of administration will differentiate the oral product from the injectable and topical products, DMETS will focus on Benadryl in its oral dosage formulation (tablets/capsules). Benadryl is indicated for the treatment of hypersensitivity reactions, motion sickness, antiparkinsonism, sleep disorders, and as an antitussive. The beginning of each name can look similar when scripted if Benadryl is scripted with a lower-case "b" and the beginning of Avandaryl is scripted with an open "A". Both names also share a similar ending ("-dryl" vs. "daryl"). Additionally, the comparable appearance in name length contributes to their orthographic similarities (8 letters vs. 9 letters).

Benadryl
Avandaryl

Benadryl and Avandaryl share an overlapping route of administration (oral), dosage form (tablet), and usual dose (1 tablet). However, both drug products differ in indication for use (hypersensitivity reactions, motion sickness, antiparkinsonism, sleep disorders, and as an antitussive vs. diabetes), strength (25 mg, 50 mg, 12 mg/5 mL, 50 mg/mL and 100 mg/5 mL vs. 4 mg/1 mg, 4 mg/2 mg, 4 mg/4 mg), and frequency of administration (every 4-6 hours and 3-4 times daily vs. once daily). Since Avandaryl is a combination product available in multiple strengths, prescriptions for Avandaryl will be strength specific. Because the rosiglitazone strength is constant in Avandaryl, prescriptions may be written based on the variable glimepiride strength (e.g., 1 mg, 2 mg, or 4 mg), which does not overlap with the strength of Avandaryl. Although Benadryl and Avandaryl share some orthographic similarities, the differentiating product characteristics (indication for use, strength, and frequency of administration) will minimize the potential for confusion and error.

DMETS also reviewed the proposed container label revisions for Avandaryl and has identified the following areas of improvement, in the interest of minimizing potential user error and improving patient safety.

A. GENERAL COMMENT



1.

yl

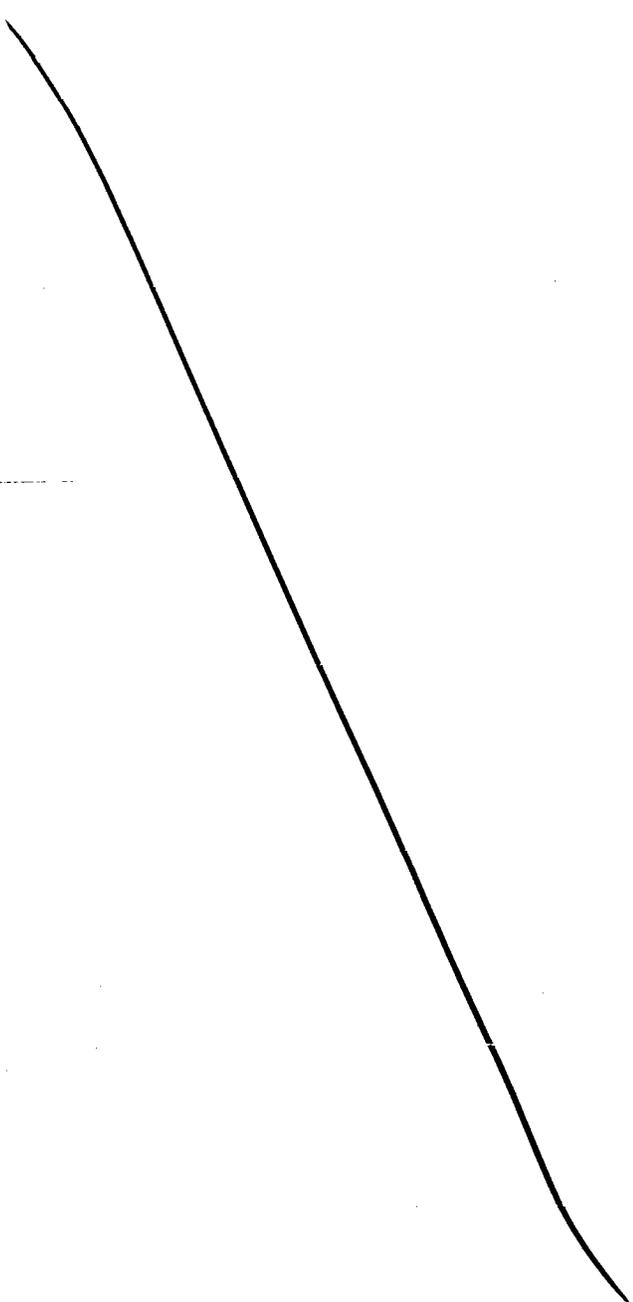
1 Page(s) Withheld

 Trade Secret / Confidential

 ✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 1



DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-0538.

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/s/

Felicia Duffy
11/17/2005 03:25:49 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
11/17/2005 03:32:11 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/17/2005 03:35:26 PM
DRUG SAFETY OFFICE REVIEWER

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/s/

David Orloff

6/30/05 04:57:16 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: August 30, 2004

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-700
Avandaryl (rosiglitazone maleate and glimepiride) tablets
GlaxoSmithKline
Treatment of type 2 diabetes

SUBJECT: NDA review issues and recommended action

Background

This is a fixed dose combination drug product of rosiglitazone (Avandia) and glimepiride (Amaryl). It is proposed for use in patients with DM2 already treated with rosiglitazone and sulfonylurea or those not adequately controlled on SFU alone. A first-line therapy indication is not sought. Rosiglitazone is already approved for concomitant use with SFU to improve glycemic control in those not adequately treated with SFU alone.

Clinical Program

Efficacy and Safety

The application contains reports of 2 new clinical trials and references 3 other trials already submitted to the Avandia NDA. A single study was conducted of Avandia plus Amaryl, while the other studies were of Avandia plus other SFU's. The totality of the clinical trial data support efficacy when Avandia is added to SFU, with absolute HbA1c lowering relative (placebo-subtracted) to SFU alone of between 0.7% and 1.4% from baseline to endpoint. No new safety issues were raised in review of the new studies.

Biopharmaceutics

A series of biopharmaceutics studies was conducted: dose-proportionality, bioequivalence of the fixed-dose product to the individual products taken in combination, a food effect study, and a drug interaction study. OCPB recommends approval.

Pharmacology/Toxicology

No additional pharm-tox data were required or submitted.

Chemistry/ Microbiology

ONDC recommends approval pending resolution of deficiencies cited after establishment inspection that lead to a Withhold recommendation from OC.

NDA # 21-700
Drug: Avandaryl
Proposal: tx DM2
08/30/04

A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

DSI/Data Integrity

No DSI audits were conducted.

Financial disclosure

The financial disclosure information is in order.

ODS/nomenclature

ODS recommends against acceptance of the proprietary name Avandaryl because of possible confusion with Avandia, Amaryl, Avandamet, and Vanceril. The confusion with other products containing rosiglitazone or with Amaryl seems likely based on name confusion and dosage strength overlap. While perhaps not engendering great clinical risk, medication errors due to such confusion would best be avoided.

Recommendation

Approvable, pending resolution of the WH recommendation for the single manufacturing site listed for this product, in Cidra, Puerto Rico. The division will work with the sponsor to address the product name issues discussed above.

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/s/

David Orloff
8/30/04 03:42:52 PM
MEDICAL OFFICER

 *** TX REPORT ***

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CONNECTION TEL		912157514096
CONNECTION ID	U. S. RA	
ST. TIME	08/26 11:46	
USAGE T	02'35	
PGS. SENT	6	
RESULT	OK	



Food and Drug Administration
 Division of Metabolic and Endocrine
 Drug Products, HFD-510
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: August 26, 2004

To: Linda Rebar	From: Lina AlJuburi
Company: GSK	Division of Metabolic and Endocrine Drug Products
Fax number: (215) 751-4926 4096	Fax number: (301) 443-9282
Phone number: (215) 751-4038	Phone number: (301) 827-6414
Subject: NDA 21-700 Avandaryl Trade Name	

Total no. of pages including cover: 6

Comments:

Document to be mailed: YES

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-700

GlaxoSmithKline
Attention: Linda Rebar
Associate Director, US Regulatory Affairs
200 North 16th Street
Philadelphia, PA 19102

Dear Ms. Rebar:

Please refer to your New Drug Application (NDA) submitted, October 31, 2003, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avandaryl (rosiglitazone maleate and glimepiride) Tablets.

We have reviewed the proposed proprietary name, AvandarylTM, and have found it unacceptable. In reviewing the proprietary name, the primary concerns related to look-alike and/or sound-alike confusion with Amaryl, Avandia and Avandamet. We are forwarding you the following comments from the Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety (ODS). Please keep these comments in mind as you make your selection of the next proposed proprietary name for rosiglitazone maleate and glimepiride tablets.

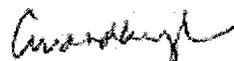
1. Amaryl may sound similar to Avandaryl. Amaryl contains one of the active ingredients in Avandaryl, glimepiride. Amaryl is in the sulfonylurea class and is indicated for the treatment of type 2 diabetes mellitus. The usual dose is 1 mg to 4 mg by mouth daily with breakfast or the first main meal. Amaryl is available as 1 mg, 2 mg, and 4 mg tablets. Amaryl sounds similar to Avandaryl because they both begin with the letter "A" and end with "aryl". In addition, Amaryl and Avandaryl rhyme with each other, thus enhancing the sound-alike qualities. Although Amaryl and Avandaryl have similar phonetic characteristics, the difference in syllables (3 syllables vs. 4 syllables) helps to phonetically differentiate them. Similarities in product characteristics include overlapping active ingredient (glimepiride), indication for use (type 2 diabetes), frequency of administration (once daily with a meal), dosage form (tablets), and patient and prescriber populations. Since the numerator in the strength of Avandaryl is constant (4 mg of rosiglitazone), it is possible that Avandaryl can be prescribed by the glimepiride strength. Post-marketing experience has shown errors occur with drug products that contain overlapping strengths, regardless of a combination ingredient versus a single ingredient. For example, Avandaryl 4 mg/1 mg, 4 mg/2 mg, and 4 mg/4 mg can be prescribed as Avandaryl

1 mg, Avandaryl 2 mg, and Avandaryl 4 mg, respectively. These strengths overlap with the strength of Amaryl (1 mg, 2 mg, and 4 mg). In these instances, the patient would not experience the benefits from rosiglitazone.

Amaryl



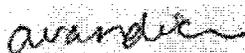
Avandaryl



Additionally, post-marketing experience also has shown cognitive errors occurring between drug products with similar names and prescriber populations. For example, due to the similarities in product names and characteristics, prescribers inadvertently write for one medication but intend another. In this case, Amaryl may be written for Avandaryl or vice versa. Overall, we believe the similarities between Amaryl and Avandaryl increase the risk of confusion and errors between the two drug products, and thus is a patient safety risk.

2. Avandia may look and sound similar to Avandaryl. Avandia contains one of the active ingredients in Avandaryl, rosiglitazone maleate. Avandia is a thiazolidinedione oral antidiabetic agent indicated for the treatment of type 2 diabetes mellitus. Avandia is available as 2 mg, 4 mg, and 8 mg tablets. The usual starting dose is 4 mg as a single daily dose or divided and administered in the morning and evening. Avandia and Avandaryl look and sound similar because they share the same prefix "Avand" and they both contain four syllables. The suffixes ("ia" vs. "aryl") give each drug name some orthographic and phonetic distinction. Although, the name Avandaryl is longer (9 letters) than the name Avandia (7 letters), Avandia and Avandaryl share the following overlapping product characteristics: active ingredient (rosiglitazone maleate), indication for use (type 2 diabetes), strength (4 mg), dosing interval (once daily), route of administration (oral), dosage form (tablet), and patient and prescriber population. Additionally, Avandia and Avandaryl will be stored in close proximity in the pharmacy. There is also the potential for computer order entry errors since the first five letters of each name is identical and the strengths are similar. If a patient receives Avandia instead of Avandaryl, he will receive only one of the two active ingredients and will likely experience hyperglycemia. We believe that the overlapping product characteristics increase the risk of confusion between Avandia and Avandaryl.

Avandia



Avandaryl



Additionally, postmarketing experience has shown that errors have occurred between drug products that contain the same root name, active ingredient and prescriber population. For example, cognitive errors have occurred where the prescriber has written for one medication, but intended another medication due to the similarities in

name and product characteristics. Furthermore, due to the overlapping product characteristics and orthographic similarities, we believe that errors will occur between Avandia and Avandaryl which can lead to a severe adverse reaction

3. Avandamet may look similar to Avandaryl when scripted. Avandamet is an oral antidiabetic agent that contains rosiglitazone maleate and metformin HCl. Avandamet is indicated for the treatment of type 2 diabetes. It is available as 1 mg/500 mg, 2 mg/500 mg, 2 mg/1000 mg, 4 mg/500 mg and 4 mg/1000 mg combination tablets. The usual starting dose is 2 mg/500 mg to 4 mg/500 mg twice daily with meals. Avandamet and Avandaryl may look similar when scripted because they both contain 9 letters, and they share the same prefix "Avanda". The last three letters of each name are different ("met" vs. "ryl"), especially the down stroke of the letter "y" in Avandaryl. Differences between Avandamet and Avandaryl include frequency of administration (twice daily with meals vs. once daily without regard to meals). Post-marketing experience has shown an error between Avandia and Avandamet where Avandia was dispensed instead of Avandamet. This report illustrates that errors can occur between combination products and the parent product that contains the single ingredient. The overlapping product characteristics are indication for use (diabetes), one active ingredient (rosiglitazone maleate), strength (4mg), route of administration (oral), dosage form (tablets), and patient and prescriber population. Avandamet and Avandaryl may have more orthographic similarity if the metformin dose in Avandamet is written in grams. For example, a prescriber may order Avandamet as 4 mg/1000 mg or 4 mg/1 gram in which the word "gram" is abbreviated as "gm" (see example below). In addition, since the denominator in the strength of Avandamet is constant (500 mg of metformin), it is possible that Avandamet can be prescribed by the rosiglitazone strength. For example, Avandamet 2 mg/500 mg and 4 mg/500 mg can be prescribed as Avandamet 2 mg and Avandamet 4 mg, respectively. Likewise, Avandaryl can be prescribed by its glimepiride component since the rosiglitazone component is constant for all strengths. Therefore, Avandaryl can be prescribed as Avandaryl 1 mg, Avandaryl 2 mg, and Avandaryl 4 mg. In this case, Avandamet and Avandaryl share an overlapping usual dose of 2 mg.

Avandamet

Avandaryl

avandamet 4mg/1gm

avandaryl 4mg/1mg

It is likely that both Avandamet and Avandaryl will be stored in closed proximity. This has the potential to cause a medication error in a busy clinic, pharmacy or inpatient unit where the wrong product can be dispensed. We are also concerned that errors will occur between Avandamet and Avandaryl with computer order entry. Since both names begin with "Avanda", and they both have rosiglitazone listed as the first active ingredient, it is likely that a computer selection error will occur. If a patient receives Avandamet instead of Avandaryl, he may experience a reaction if he is sensitive to metformin. He may also become hypoglycemic if the misfilled Avandamet is taken without a meal, which can be life threatening to a brittle diabetic. We are also concerned about the potential for cognitive errors between Avandamet

and Avandaryl. Since both products have the same prescriber population, indication for use, active ingredient, and similar names, post-marketing experience has shown cognitive errors occurring where the health care provider inadvertently writes one product, but intends another. Due to the overlapping product characteristics and orthographic similarities, we believe that errors will occur between Avandamet and Avandaryl which can lead to a severe adverse reaction.

If you have any questions, call Lina AlJuburi, Regulatory Project Manager, at 301-827-6414.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.

Director

Division of Metabolic and Endocrine Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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

/s/

David Orloff
8/25/04 10:20:03 PM



NDA 21-700

DISCIPLINE REVIEW LETTER

GlaxoSmithKline
Attention: Justin Geiger
Assistant Director, Global CMC Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA 19426

Dear Mr. Geiger:

Please refer to your October 31, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avandaryl (rosiglitazone maleate and glimepiride) Tablets.

We also refer to the discipline review letter we issued to you on August 12, 2004, which had two typographical errors regarding the dissolution method conditions for Avandaryl Tablets.

The accurate comment regarding dissolution method conditions for Avandaryl Tablets is the following:

**The solubility of both rosiglitazone and glimepiride is highly pH dependent. The dissolution media of 0.01 M HCl is acceptable with 0.5% SDS at a paddle speed of 75 rpm. The agreed specifications for dissolution are as follows:
Specification limit: Q = ~~—~~ at 15 min for rosiglitazone dissolution, and
Q = ~~—~~ at 45 min for glimepiride dissolution.**

Labeling comments will be conveyed in future correspondences.

If you have any questions, call Lina AlJuburi, Regulatory Project Manager, at 301-827-6414.

Sincerely,

{See appended electronic signature page}

David Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

David Orloff

8/25/04 10:17:46 PM

Aljuburi, Lina

From: Folkendt, Michael M
Sent: Wednesday, August 18, 2004 2:10 PM
To: Ysern, Xavier J; Johnson, Kati; Duffy, Eric P; Moore, Stephen K
Cc: Aljuburi, Lina
Subject: RE: NDA 21-700 (Resent with Corrections)

The overall recommendation is set to withhold now.

-----Original Message-----

From: Ysern, Xavier J
Sent: Thursday, August 12, 2004 1:13 PM
To: Johnson, Kati; Folkendt, Michael M; Duffy, Eric P; Moore, Stephen K
Cc: Aljuburi, Lina
Subject: RE: NDA 21-700 (Resent with Corrections)

As mentioned in one of my previous e-mails, there are no alternate DP manufacturing facilities for this [convenience] product.
Xavier

-----Original Message-----

From: Johnson, Kati
Sent: Thursday, August 12, 2004 1:09 PM
To: Folkendt, Michael M; Duffy, Eric P; Ysern, Xavier J; Moore, Stephen K
Cc: Aljuburi, Lina
Subject: RE: NDA 21-700 (Resent with Corrections)

1. yep.
2. this is a convenience dosage form of 2 already AP medicines. So unless you count having to take 2 tablets instead of 1, there is no health crisis.
3. can't answer this. Xavier, Steve????

KJ

-----Original Message-----

From: Folkendt, Michael M
Sent: Thursday, August 12, 2004 8:55 AM
To: Johnson, Kati; Duffy, Eric P; Ysern, Xavier J; Moore, Stephen K
Cc: Aljuburi, Lina
Subject: RE: NDA 21-700 (Resent with Corrections)

Kati,

If this inspection was not an issue, would the Division approve the NDA? Would not approving the NDA cause a health care or other crisis? Is there an alternate to this PR facility in the NDA?

Michael

-----Original Message-----

From: Johnson, Kati
Sent: Thursday, August 12, 2004 5:48 AM
To: Duffy, Eric P; Ysern, Xavier J; Moore, Stephen K
Cc: Aljuburi, Lina; Folkendt, Michael M
Subject: RE: NDA 21-700 (Resent with Corrections)

So, given that it appears that the EER will NOT be completed by the goal date (8/31/04), we will take an AE action?? or go overdue?? Please cast your vote. We will brief David when he returns on Monday.

Michael-thanks very much for your help on this.

Kati

-----Original Message-----

From: Duffy, Eric P
Sent: Wednesday, August 11, 2004 3:34 PM
To: Ysern, Xavier J; Moore, Stephen K; Johnson, Kati
Subject: FW: NDA 21-700 (Resent with Corrections)

Here is the OC response. Has there been an overall OC recommendation?

- Eric

Eric P. Duffy, Ph.D.

Director
Division of New Drug Chemistry II
FDA/OPS/CDER/ONDC/DNDCH
5600 Fishers Lane, HFD-820, Rm. 9B-23
Rockville, MD 20852
Office: 301-827-1049 Fax: 301-594-6071
duffy@cder.fda.gov

-----Original Message-----

From: Rivera Martinez, Edwin
Sent: Wednesday, August 11, 2004 3:06 PM
To: Folkendt, Michael M
Cc: Duffy, Eric P; Famulare, Joseph; Buhay, Nicholas; Blumenschein, Frederick W; Lopez, Teddi; Rothman, Barry; Brown, Raymond L; Ferguson, Shirnette D
Subject: NDA 21-700 (Resent with Corrections)

Michael:

This is in response to your telephone message this morning regarding GlaxoSmithKline's NDA 21-700 for Rosiglitazone Maleate/Glimepiride tablets and the review division's request to review the FD-483. The facility identified in the EER, SmithKline Beecham Pharmaceuticals Co., Cidra, PR (CFN 2658115) was the subject of a recommendation for permanent injunction from San Juan District due to systematic CGMP deviations found during repeated inspections of the Cidra facility, the most recent conducted during October 7 - December 2, 2003. 'S

DMPQ's Case Management and Guidance Branch reviewed the injunction recommendation and meet with GlaxoSmithKline officials on May 14, 2004, to discuss the latest inspection and the firm's corrective actions. We concluded on July 8 that while there are many potentially serious CGMP deviations at this facility, a reinspection is needed before OC can consider approving the injunction recommendation. We checked with San Juan District and they tentatively plan to initiate a comprehensive CGMP reinspection of the Cidra site the first or second week of September 2004. If reinspection reveals the firm has not implemented their promised corrections and serious deviations persist, OC will entertain an updated injunction recommendation or other regulatory action.

Please contact me if you have any questions or if I can be of further assistance.

Edwin Rivera Martínez

Chief

Investigations and Preapproval Compliance Branch, HFD-322

Division of Manufacturing and Product Quality

Office of Compliance

Center for Drug Evaluation and Research

Telephone: (301) 827-9012

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On Original**



Memorandum

Date: July 21, 2004

To: File, NDA 21-700

Through: Lina AlJuburi, Project Manager , HFD-510

From: Jeri ElHage, Ph.D., Pharmacology Supervisor
DMEDP, HFD-510, CDER

Subject: Waiver of Pharmacology/Toxicology Review for NDA 21-700

NDA 21-700 seeks marketing approval for the new combination drug product Avandaryl which is composed of the two approved drugs rosiglitazone (NDA 21-071) and glimepiride (NDA 20-496). Complete pharmacological and toxicological evaluations were performed for each of the approved drug products and the data are cross-referenced in this application. No new nonclinical information was provided in this NDA for Avandaryl and, therefore, a pharmacology review of this application is not warranted.

The nonclinical sections of the labeling including the mutagenesis, carcinogenesis and impairment of fertility and pregnancy category labeling should reflect the verbatim approved labeling for both products.

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/s/

Jeri El Hage
7/21/04 12:01:33 PM
PHARMACOLOGIST

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: 2/17/04 **DESIRED COMPLETION DATE:** 6/30/04 **ODS CONSULT #:** 04-0051

TO: David Orloff, MD
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: Lina AlJuburi
Project Manager
HFD-510

PRODUCT NAME:
Avandaryl™
(Rosiglitazone Maleate and Glimepiride) Tablets
4 mg/1 mg, 4 mg/2 mg, and 4 mg/4 mg

NDA SPONSOR: GlaxoSmithKline

NDA#: 21-700

SAFETY EVALUATOR: Felicia Duffy, RN

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, Avandaryl.

DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Avandaryl acceptable from a promotional perspective.

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)

Office of Drug Safety

HFD-420; PKLN Rm. 6-34

Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 8, 2004

NDA# 21-700

NAME OF DRUG: Avandaryl™
(Rosiglitazone Maleate and Glimepiride) Tablets
4 mg/1 mg, 4 mg/2 mg, and 4 mg/4 mg

NDA HOLDER: GlaxoSmithKline

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), for assessment of the proprietary name, "Avandaryl", regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Avandaryl (rosiglitazone maleate and glimepiride) contains two oral antihypoglycemic drugs, rosiglitazone maleate and glimepiride. Rosiglitazone maleate is from the thiazolidinedione class of antidiabetic agents and glimepiride is in the sulfonylurea class of antidiabetic agents. Avandaryl is indicated as an adjunct treatment to diet and exercise to improve glycemic control in type 2 diabetic patients who are already treated with a combination of thiazolidinedione and sulfonylurea or patients who are not adequately controlled with thiazolidinedione or sulfonylurea alone. Avandaryl will be available as a combination tablet containing a fixed dose of 4 mg rosiglitazone with variable doses of glimepiride (1 mg, 2 mg, or 4 mg) in a single tablet formulation. Avandaryl will be given once daily with a meal. The dosage will be individualized with each patient. For patients inadequately controlled on thiazolidinedione or sulfonylurea monotherapy, the usual starting dose of Avandaryl is 4 mg/1 mg, or 4 mg/2 mg once daily. The usual starting dose of Avandaryl when switching from combination therapy of rosiglitazone plus glimepiride as separate tablets, is the dose of rosiglitazone and glimepiride already being taken. The maximum recommended daily dose of Avandaryl is 4 mg of rosiglitazone and 4 mg of glimepiride.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2}, as well as several FDA databases³ for existing drug names which sound-alike or

¹ MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

look-alike to Avandaryl to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Avandaryl. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Avandaryl acceptable from a promotional perspective.
2. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Avandaryl. These products are listed in table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Avandaryl	Rosiglitazone Maleate and Glimepiride Tablets: 4 mg/1 mg, 4 mg/2 mg, and 4 mg/4 mg	Initial Therapy: 4 mg/1 mg or 4 mg/2mg QD with a meal Maximum Dose: 4 mg/4 mg QD	
Vanceril	Beclomethasone Dipropionate Inhalation aerosol: 42 mcg/inhalation	2 oral inhalations three or four times daily.	SA
Amaryl	Glimepiride Tablets: 1 mg, 2 mg, and 4 mg	1 mg to 4 mg QD with breakfast or the first main meal.	SA
Avandia	Rosiglitazone Maleate Tablets: 2 mg, 4 mg, and 8 mg	Initial Therapy: 4 mg QD or 2 mg BID. Maximum Dose: 8 mg QD or in divided doses twice daily. May be given without regard to meals.	SA/LA
Avandamet	Rosiglitazone Maleate and Metformin HCl Tablets: 1 mg/500 mg, 2 mg/500 mg, 4 mg/500 mg, 2 mg/1000 mg, and 4 mg/1000 mg	Initial Therapy: 2 mg/500 mg to 4 mg/500 mg BID with meals. Maximum Dose: 8 mg/2000 mg, in divided doses with meals.	LA
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike)			

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

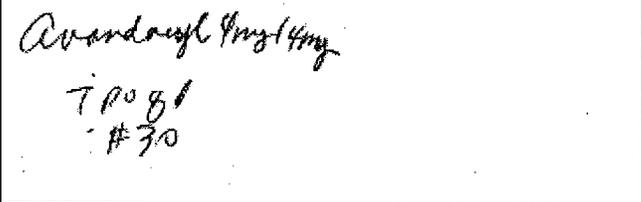
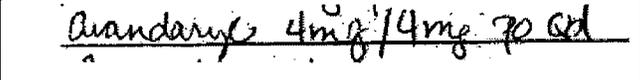
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Avandaryl were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Avandaryl with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Avandaryl (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> 	<p>Avandaryl 4mg/4 mg Sig: Take one by mouth every day Dispense 30</p>
<p>Inpatient RX:</p> 	

2. Results:

One respondent interpreted the proposed name as Avandia, a currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

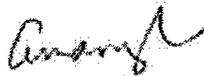
E. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Avandaryl, the primary concerns related to look-alike and sound-alike confusion with Vanceril, Amaryl, Avandia, and Avandamet. The tool also identified the aforementioned names as having significant phonetic or orthographic similarity. Upon review of the names gathered from , the name Vanceril was not reviewed further due to a lack of convincing look-alike/sound-alike similarities with Avandaryl in addition to numerous differentiating product characteristics such as the strength, indication for use, frequency of administration, route of administration and dosage form.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Avandia could be confused with Avandaryl. One respondent from the Avandaryl verbal study misinterpreted the name for Avandia, an already marketed drug product. Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

1. Amaryl may sound similar to Avandaryl. Amaryl contains one of the active ingredients in Avandaryl, glimepiride. Amaryl is in the sulfonylurea class and is indicated for the treatment of type 2 diabetes mellitus. The usual dose is 1 mg to 4 mg by mouth daily with breakfast or the first main meal. Amaryl is available as 1 mg, 2 mg, and 4 mg tablets. Amaryl sounds similar to Avandaryl because they both begin with the letter "A" and end with "aryl". In addition, Amaryl and Avandaryl rhyme with each other, thus enhancing the sound-alike qualities. Although Amaryl and Avandaryl have similar phonetic characteristics, the difference in syllables (3 syllables vs. 4 syllables) helps to phonetically differentiate them. Similarities in product characteristics include overlapping active ingredient (glimepiride), indication for use (type 2 diabetes), frequency of administration (once daily with a meal), dosage form (tablets), and patient and prescriber populations. Since the numerator in the strength of Avandaryl is constant (4 mg of rosiglitazone), it is possible that Avandaryl can be prescribed by the glimepiride strength. Post-marketing experience has shown errors occur with drug products that contain overlapping strengths, regardless of a combination ingredient versus a single ingredient. For example, Avandaryl 4 mg/1 mg, 4 mg/2 mg, and 4 mg/4 mg can be prescribed as Avandaryl 1 mg, Avandaryl 2 mg, and Avandaryl 4 mg, respectively. These strengths overlap with the strength of Amaryl (1 mg, 2 mg, and 4 mg). In these instances, the patient would not experience the benefits from rosiglitazone.

Amaryl



Avandaryl



Additionally, post-marketing experience also has shown cognitive errors occurring between drug products with similar names and prescriber populations. For example, due to the similarities in product names and characteristics, prescribers inadvertently write for one medication but intend another. In this case, Amaryl may be written for Avandaryl or vice versa. Overall, DMETS believes the similarities between Amaryl and Avandaryl increase the risk of confusion and errors between the two drug products, and thus is a patient safety risk.

2. Avandia may look and sound similar to Avandaryl. Avandia contains one of the active ingredients in Avandaryl, rosiglitazone maleate. Avandia is a thiazolidinedione oral antidiabetic agent indicated for the treatment of type 2 diabetes mellitus. Avandia is available as 2 mg, 4mg, and 8 mg tablets. The usual starting dose is 4 mg as a single daily dose or divided and administered in the morning and evening. Avandia and Avandaryl look and sound similar because they share the same prefix “Avand” and they both contain four syllables. The suffixes (“ia” vs. “aryl”) give each drug name some orthographic and phonetic distinction. Although, the name Avandaryl is longer (9 letters) than the name Avandia (7 letters), Avandia and Avandaryl share the following overlapping product characteristics: active ingredient (rosiglitazone maleate), indication for use (type 2 diabetes), strength (4 mg), dosing interval (once daily), route of administration (oral), dosage form (tablet), and patient and prescriber population. Additionally, Avandia and Avandaryl will be stored in close proximity in the pharmacy. There is also the potential for computer order entry errors since the first five letters of each name is identical and the strengths are similar. If a patient receives Avandia instead of Avandaryl, he will receive only one of the two active ingredients and will likely experience hyperglycemia. DMETS believes that the overlapping product characteristics increase the risk of confusion between Avandia and Avandaryl.

Avandia

Avandaryl

avandia

avandaryl

Additionally, postmarketing experience has shown that errors have occurred between drug products that contain the same root name, active ingredient and prescriber population. For example, cognitive errors have occurred where the prescriber has written for one medication, but intended another medication due to the similarities in name and product characteristics. Furthermore, due to the overlapping product characteristics and orthographic similarities, DMETS believes that errors will occur between Avandia and Avandaryl which can lead to a severe adverse reaction

3. Avandamet may look similar to Avandaryl when scripted. Avandamet is an oral antidiabetic agent that contains rosiglitazone maleate and metformin HCl. Avandamet is indicated for the treatment of type 2 diabetes. It is available as 1 mg/500 mg, 2 mg/500 mg, 2 mg/1000 mg, 4 mg/500 mg and 4 mg/1000 mg combination tablets. The usual starting dose is 2 mg/500 mg to 4 mg/500 mg twice daily with meals. Avandamet and Avandaryl may look similar when scripted because they both contain 9 letters, and they share the same prefix “Avanda”. The last three letters of each name are different (“met” vs. “ryl”), especially the downstroke of the letter “y” in Avandaryl. Differences between Avandamet and Avandaryl include frequency of administration (twice daily with meals vs. once daily without regard to meals). Post-marketing experience has shown an error between Avandia and Avandamet where Avandia was dispensed instead of Avandamet. This report illustrates that errors can occur between combination products and the parent product that contains the single ingredient. The overlapping product characteristics are indication for use (diabetes), one active ingredient (rosiglitazone maleate), strength (4mg), route of administration (oral), dosage form (tablets), and patient and prescriber population. Avandamet and Avandaryl may have more orthographic similarity if the metformin dose in Avandamet is written in grams. For example, a prescriber may order Avandamet as 4 mg/1000 mg or 4 mg/1 gram in which the word “gram” is abbreviated as “gm” (see example on page 7). In addition, since the

denominator in the strength of Avandamet is constant (500 mg of metformin), it is possible that Avandamet can be prescribed by the rosiglitazone strength. For example, Avandamet 2 mg/500 mg and 4 mg/500 mg can be prescribed as Avandamet 2 mg and Avandamet 4 mg, respectively. Likewise, Avandaryl can be prescribed by its glimepiride component since the rosiglitazone component is constant for all strengths. Therefore, Avandaryl can be prescribed as Avandaryl 1 mg, Avandaryl 2 mg, and Avandaryl 4 mg. In this case, Avandamet and Avandaryl share an overlapping usual dose of 2 mg.

Avandamet

avandamet 4mg/500mg

Avandaryl

avandaryl 4mg/1mg

It is likely that both Avandamet and Avandaryl will be stored in closed proximity. This has the potential to cause a medication error in a busy clinic, pharmacy or inpatient unit where the wrong product can be dispensed. DMETS is also concerned that errors will occur between Avandamet and Avandaryl with computer order entry. Since both names begin with "Avanda", and they both have rosiglitazone listed as the first active ingredient, it is likely that a computer selection error will occur. If a patient receives Avandamet instead of Avandaryl, he may experience a reaction if he is sensitive to metformin. He may also become hypoglycemic if the misfilled Avandamet is taken without a meal, which can be life threatening to a brittle diabetic. DMETS is also concerned about the potential for cognitive errors between Avandamet and Avandaryl. Since both products have the same prescriber population, indication for use, active ingredient, and similar names, post-marketing experience has shown cognitive errors occurring where the health care provider inadvertently writes one product, but intends another. Due to the overlapping product characteristics and orthographic similarities, DMETS believes that errors will occur between Avandamet and Avandaryl which can lead to a severe adverse reaction.

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name Avandaryl. In reviewing the proprietary name, the primary concerns related to look-alike and/or sound-alike confusion with Amaryl, Avandia and Avandamet. Additionally, DMETS reviewed the labels and labeling from a safety perspective. DMETS has identified several areas of possible improvement, which might minimize potential user error.

1. Amaryl may sound similar to Avandaryl. Amaryl contains one of the active ingredients in Avandaryl, glimepiride. Amaryl is in the sulfonylurea class and is indicated for the treatment of type 2 diabetes mellitus. The usual dose is 1 mg to 4 mg by mouth daily with breakfast or the first main meal. Amaryl is available as 1 mg, 2 mg, and 4 mg tablets. Amaryl sounds similar to Avandaryl because they both begin with the letter "A" and end with "aryl". In addition, Amaryl and Avandaryl rhyme with each other, thus enhancing the sound-alike qualities. Although Amaryl and Avandaryl have similar phonetic characteristics, the difference in syllables (3 syllables vs. 4 syllables) helps to phonetically differentiate them. Similarities in product characteristics include overlapping active ingredient (glimepiride), indication for use (type 2 diabetes), frequency of administration (once daily with a meal), dosage form (tablets), and patient and prescriber populations. Since the numerator in the strength of Avandaryl is constant (4 mg of rosiglitazone), it is possible that Avandaryl can be prescribed by the glimepiride strength. Post-marketing experience has shown errors occur with drug products that contain overlapping strengths, regardless of a combination ingredient versus a single ingredient. For example, Avandaryl 4 mg/1 mg, 4 mg/2 mg,

and 4 mg/4 mg can be prescribed as Avandaryl 1 mg, Avandaryl 2 mg, and Avandaryl 4 mg, respectively. These strengths overlap with the strength of Amaryl (1 mg, 2 mg, and 4 mg). In these instances, the patient would not experience the benefits from rosiglitazone.

Amaryl

Avandaryl

Additionally, post-marketing experience also has shown cognitive errors occurring between drug products with similar names and prescriber populations. For example, due to the similarities in product names and characteristics, prescribers inadvertently write for one medication but intend another. In this case, Amaryl may be written for Avandaryl or vice versa. Overall, DMETS believes the similarities between Amaryl and Avandaryl increase the risk of confusion and errors between the two drug products, and thus is a patient safety risk.

2. Avandia may look and sound similar to Avandaryl. Avandia contains one of the active ingredients in Avandaryl, rosiglitazone maleate. Avandia is a thiazolidinedione oral antidiabetic agent indicated for the treatment of type 2 diabetes mellitus. Avandia is available as 2 mg, 4mg, and 8 mg tablets. The usual starting dose is 4 mg as a single daily dose or divided and administered in the morning and evening. Avandia and Avandaryl look and sound similar because they share the same prefix “Avand” and they both contain four syllables. The suffixes (“ia” vs. “aryl”) give each drug name some orthographic and phonetic distinction. Although, the name Avandaryl is longer (9 letters) than the name Avandia (7 letters), Avandia and Avandaryl share the following overlapping product characteristics: active ingredient (rosiglitazone maleate), indication for use (type 2 diabetes), strength (4 mg), dosing interval (once daily), route of administration (oral), dosage form (tablet), and patient and prescriber population. Additionally, Avandia and Avandaryl will be stored in close proximity in the pharmacy. There is also the potential for computer order entry errors since the first five letters of each name is identical and the strengths are similar. If a patient receives Avandia instead of Avandaryl, he will receive only one of the two active ingredients and will likely experience hyperglycemia. DMETS believes that the overlapping product characteristics increase the risk of confusion between Avandia and Avandaryl.

Avandia

Avandaryl

Additionally, postmarketing experience has shown that errors have occurred between drug products that contain the same root name, active ingredient and prescriber population. For example, cognitive errors have occurred where the prescriber has written for one medication, but intended another medication due to the similarities in name and product characteristics. Furthermore, due to the overlapping product characteristics and orthographic similarities, DMETS believes that errors will occur between Avandia and Avandaryl which can lead to a severe adverse reaction

3. Avandamet may look similar to Avandaryl when scripted. Avandamet is an oral antidiabetic agent that contains rosiglitazone maleate and metformin HCl. Avandamet is indicated for the treatment of type 2 diabetes. It is available as 1 mg/500 mg, 2 mg/500 mg, 2 mg/1000 mg, 4 mg/500 mg and 4 mg/1000 mg combination tablets. The usual starting dose is 2 mg/500 mg to 4 mg/500 mg twice daily with meals. Avandamet and Avandaryl may look similar when scripted because they both contain 9 letters, and they share the same prefix “Avanda”. The last three letters

of each name are different (“met” vs. “ryl”), especially the downstroke of the letter “y” in Avandaryl. Differences between Avandamet and Avandaryl include frequency of administration (twice daily with meals vs. once daily without regard to meals). Post-marketing experience has shown an error between Avandia and Avandamet where Avandia was dispensed instead of Avandamet. This report illustrates that errors can occur between combination products and the parent product that contains the single ingredient. The overlapping product characteristics are indication for use (diabetes), one active ingredient (rosiglitazone maleate), strength (4mg), route of administration (oral), dosage form (tablets), and patient and prescriber population. Avandamet and Avandaryl may have more orthographic similarity if the metformin dose in Avandamet is written in grams. For example, a prescriber may order Avandamet as 4 mg/1000 mg or 4 mg/1 gram in which the word “gram” is abbreviated as “gm” (see example below). In addition, since the denominator in the strength of Avandamet is constant (500 mg of metformin), it is possible that Avandamet can be prescribed by the rosiglitazone strength. For example, Avandamet 2 mg/500 mg and 4 mg/500 mg can be prescribed as Avandamet 2 mg and Avandamet 4 mg, respectively. Likewise, Avandaryl can be prescribed by its glimepiride component since the rosiglitazone component is constant for all strengths. Therefore, Avandaryl can be prescribed as Avandaryl 1 mg, Avandaryl 2 mg, and Avandaryl 4 mg. In this case, Avandamet and Avandaryl share an overlapping usual dose of 2 mg.

Avandamet

avandamet 4mg/1gm

Avandaryl

avandaryl 4mg/1mg

It is likely that both Avandamet and Avandaryl will be stored in closed proximity. This has the potential to cause a medication error in a busy clinic, pharmacy or inpatient unit where the wrong product can be dispensed. DMETS is also concerned that errors will occur between Avandamet and Avandaryl with computer order entry. Since both names begin with “Avanda”, and they both have rosiglitazone listed as the first active ingredient, it is likely that a computer selection error will occur. If a patient receives Avandamet instead of Avandaryl, he may experience a reaction if he is sensitive to metformin. He may also become hypoglycemic if the misfilled Avandamet is taken without a meal, which can be life threatening to a brittle diabetic. DMETS is also concerned about the potential for cognitive errors between Avandamet and Avandaryl. Since both products have the same prescriber population, indication for use, active ingredient, and similar names, post-marketing experience has shown cognitive errors occurring where the health care provider inadvertently writes one product, but intends another. Due to the overlapping product characteristics and orthographic similarities, DMETS believes that errors will occur between Avandamet and Avandaryl which can lead to a severe adverse reaction.

In the review of the container labels, carton and insert labeling of Avandaryl, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS



1 Page(s) Withheld

 Trade Secret / Confidential

 ✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 2

V. RECOMMENDATIONS:

- A. DMETS does not recommend the use of the proprietary name Avandaryl.
- B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary name Avandaryl acceptable from a promotional perspective

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Felicia Duffy, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Felicia Duffy
7/1/04 06:40:41 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
7/1/04 12:23:02 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/1/04 03:02:54 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: May 27, 2004

TO: David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
HFD-510

VIA: Lina AlJuburi, Regulatory Health Project Manager,
Division of Metabolic and Endocrine Drug Products
HFD-510

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of the Patient Labeling for Avandaryl
(rosiglitazone maleate and glimepiride) Tablets, NDA 21-700

The attached patient labeling represents the revised risk communication materials for Avandaryl (rosiglitazone maleate and glimepiride) Tablets, NDA 21-700. It has been reviewed by our office and by DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. These revisions are based on draft labeling submitted by the sponsor October 13, 2003. Patient information should always be consistent with the prescribing information. All future changes to the PI should also be reflected in the PPI.

Comments to the review division are bolded, underlined and italicized. We can provide a marked-up and clean copy of the revised document in Word if requested by the review division. Please call us if you have any questions.

5 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 3

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/s/

Jeanine Best
5/27/04 02:24:04 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
5/28/04 04:14:01 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan



NDA 21-700

INFORMATION REQUEST LETTER

GlaxoSmithKline
Attention: Justin Geiger
Assistant Director, Global CMC Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA 19426

Dear Mr. Geiger:

Please refer to your May 13, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avandaryl (rosiglitazone maleate and glimepiride) Tablets.

We are reviewing the Clinical Pharmacology and Biopharmaceutics 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. We believe the SDS at 75 rpm is too rigorous and the use of 0.01 M HCl 0.5% SDS at 75 rpm is recommended. However, the data included is only from one lot. Therefore, please submit dissolution data using the Agency's proposed method for two additional lots to set the specifications. Include clinical and to be marketed lots for this study.
2. Submit the above dissolution data for all the three strengths that are to be marketed.
3. Additionally, include the similarity factor between each strength for the requested biowaiver.

If you have any questions, call Lina AlJuburi, Regulatory Project Manager, at 301-827-6414.

Sincerely,

{See appended electronic signature page}

David Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
5/27/04 05:34:35 PM



MEMORANDUM

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

DATE: May 3, 2004

TO: David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products, HFD-510

FROM: Office of Drug Safety

Mark Avigan, M.D., Director
Division of Drug Risk Evaluation, HFD-430

Carol Holquist, RPh., Director
Division of Medication Error and Technical Support, HFD-420

Gerald DalPan, MD, MHS, Director
Division of Surveillance, Research and Communication Support, HFD-410

SUBJECT: ODS Review of Proposed Risk Management Plan (RMP) for Avandaryl™
(rosiglitazone maleate/glimepiride; NDA 21-700); submitted October 31,
2003

PID #: D040093

The sponsor's proposed Risk Management Plan does not appear to differ substantially from a typical new product labeling and routine passive post-marketing safety surveillance.

Avandaryl® is a combination product containing the active ingredients rosiglitazone maleate (4mg) and glimepiride (1, 2, or 4mg), approved products already on the U.S. market. The proposed indication is as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. There does not appear to be any unique safety issues with the combination product and neither of the two marketed products require risk management tools beyond standard product labeling.

The Office of Drug Safety has reviewed the submitted RMP and has determined that it does not identify a specific safety concern for which a RMP to minimize risk would be normally associated. The sponsor proposes a Patient Package Insert which is currently under review by the Division of Surveillance, Research, and Communication Support in the Office of Drug Safety.

Mark Avigan, M.D., Director
Division of Drug Risk Evaluation, HFD-430

Carol Holquist, RPh., Director
Division of Medication Error and Technical Support, HFD-420

Gerald DalPan, M.D., Director
Division of Surveillance, Research and Communication Support, HFD-410

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/s/

Mary Dempsey
5/3/04 10:22:26 AM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
5/3/04 01:28:49 PM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
5/4/04 03:15:07 PM
MEDICAL OFFICER

Carol Holquist
5/4/04 04:01:01 PM
DRUG SAFETY OFFICE REVIEWER



NDA 21-700

INFORMATION REQUEST LETTER

GlaxoSmithKline
Attention: Justin Geiger
Assistant Director, Global CMC Regulatory Affairs
1250 South Collegeville Road
P.O. Box 5089 (Mail Code UP4210)
Collegeville, PA 19426

Dear Mr. Geiger:

Please refer to your October 31, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avandaryl (rosiglitazone maleate and glimepiride) Tablets; 4mg/1mg, 4mg/2mg, 4mg/4mg.

We also refer to your submission dated March 31, 2004.

We are reviewing the Biopharmaceutical 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.

We agree with the dissolution medium of 0.01 M HCl. However, please justify the use of ~~0.5%~~ SDS at the paddle speed of 75 rpm. Based on the dissolution data provided, greater than ~~50%~~ of both rosiglitazone maleate and glimepiride is dissolved within ~~15~~ min. Therefore, this dissolution method appears to be too rigorous. Please provide dissolution data using 0.5% SDS at 75 rpm ~~at 75 rpm~~

If you have any questions, call Lina AlJuburi, Regulatory Project Manager, at 301-827-6414.

Sincerely,

{See appended electronic signature page}

David Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff

4/13/04 10:15:37 AM

NDA REGULATORY FILING REVIEW
(Memo of Filing Meeting Included)

NDA #: 21-700

Original NDA Submission

Trade Name: Avandaryl Tablets

Generic Name: rosiglitazone maleate and glimepiride

Strengths: 4 mg/1 mg; 4 mg/2 mg; 4 mg/4 mg

Applicant: GlaxoSmithKline

Date of Application: October 31, 2003

Date of Receipt: October 31, 2003

Date clock started after UN: N/A

Date of Filing Meeting: meeting not held

Filing Date: December 30, 2003

Action Goal Date (optional): TBD

User Fee Goal Date: August 31, 2004

Indication(s) requested: Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of thiazolidinedione and sulfonylurea or who are not adequately controlled on a thiazolidinedione or sulfonylurea alone.

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

Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE: 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) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S X P _____
Resubmission after withdrawal? NO Resubmission after refuse to file? NO
Chemical Classification: (1,2,3 etc.) 4
Other (orphan, OTC, etc.) NO

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

Form 3397 (User Fee Cover Sheet) submitted: YES

User Fee ID # 4613
Clinical data? YES X NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

 NO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? 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

Is the application affected by the Application Integrity Policy (AIP)?
If yes, explain. NO

If yes, has OC/DMPQ been notified of the submission? N/A

• Does the submission contain an accurate comprehensive index? YES

• Was form 356h included with an authorized signature? YES

If foreign applicant, both the applicant and the U.S. agent must sign.

• Submission complete as required under 21 CFR 314.50? YES

If no, explain:

• If an electronic NDA, does it follow the Guidance? YES

If an electronic NDA, all certifications must be in paper and require a signature.

Which parts of the application were submitted in electronic format?

Additional comments:

• If in Common Technical Document format, does it follow the guidance? YES

• Is it an electronic CTD? NO

If an electronic CTD, all certifications must be in paper and require a signature.

Which parts of the application were submitted in electronic format?

Additional comments:

• Patent information submitted on form FDA 3542a? YES

- Exclusivity requested? **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**

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**

(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? **YES**

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? **YES**
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections. **YES**

- List referenced IND numbers: **66,162**

- End-of-Phase 2 Meeting(s)? Date(s) **NONE**

If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) **June 2, 2003**

If yes, distribute minutes before filing meeting.

Project Management

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

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

If Rx-to-OTC Switch application: N/A

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
- Has DOTCDP been notified of the OTC switch application?

Clinical:

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

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

If 505(b)(2) application, complete the following section: N/A

- Name of listed drug(s) and NDA/ANDA #:
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the

application should be refused for filing under 314.101(d)(9).

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

___ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

___ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

___ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

___ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

___ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

___ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?)

N/A YES NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

 - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

 - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

 - EITHER
 The number of the applicant's IND under which the studies essential to approval were conducted.

IND # _____ NO

OR

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT

MEMO OF FILING MEETING

No filing meeting. No filing issues. NDA filed December 30, 2003. Information was requested from the sponsor by the biopharmaceutics reviewer in the 74-day letter issued on January 6, 2004.

DATE:

BACKGROUND:

(Provide a brief background of the drug, e.g., it was already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES:

ASSIGNED REVIEWERS:

Discipline: Reviewer

Medical: J. Zawadzki

Secondary Medical: none

Statistical: T. Sahlroot

Pharmacology: J. El Hage

Statistical Pharmacology: none

Chemistry: X. Ysern

Environmental Assessment (if needed): TBD

Biopharmaceutical: J. Vaidyanathan

Microbiology: none needed

Microbiology, clinical (for antimicrobial products only): none needed

DSI: TBD

Regulatory Project Management: L. AlJuburi

Other Consults:

- Trade name review consult (contact person is Sammie Beam)
- Risk management plan consult (contact person is Mary Dempsey)

Per reviewers, are all parts in English or English translation?

If no, explain:

CLINICAL

FILE _____

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known _____
NO

- 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 YES NO

CLINICAL MICROBIOLOGY NA _____ FILE _____ REFUSE TO FILE

STATISTICS FILE _____ REFUSE TO FILE

BIOPHARMACEUTICS FILE _____ REFUSE TO FILE

- Biopharm. inspection needed: YES NO

PHARMACOLOGY NA _____ FILE _____ REFUSE TO FILE

- GLP inspection needed: YES NO

CHEMISTRY FILE _____ REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:

Any comments: CTD format

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ 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 the 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. Document filing issues/no filing issues conveyed to applicant by Day 74.

Lina AlJuburi, PharmD., M.S.
Regulatory Project Manager, HFD-510

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

/s/

Lina Aljuburi
2/19/04 03:38:30 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-700

GlaxoSmithKline
Attention: Linda Rebar
Associate Director, US Regulatory Affairs
200 N. 16th Street
Philadelphia, PA 19102

Dear Ms. Rebar:

Please refer to your October 31, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avandaryl (rosiglitazone maleate and glimepiride) Tablets; 4 mg/1 mg, 4 mg/2 mg, 4 mg/4 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on December 30, 2003 in accordance with 21 CFR 314.101(a).

We request that you submit dissolution profiles in 3 different conditions, using 3 lots (12/units/lot) in each test condition.

Please respond only to the above request 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 Lina AlJuburi, Regulatory Project Manager, at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

Kati Johnson, R.Ph.
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lina Aljuburi
1/6/04 12:05:20 PM
on behalf of Kati Johnson



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-700

GlaxoSmithKline
Attention: Linda Rebar
Associate Director, US Regulatory Affairs
200 N. 16th Street
Philadelphia, PA 19102

Dear Ms. Rebar:

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

Name of Drug Product: Avandaryl (rosiglitazone maleate and glimepiride) Tablets;
4 mg/1 mg, 4 mg/2 mg, 4 mg/4 mg

Review Priority Classification: Standard (S)

Date of Application: October 31, 2003

Date of Receipt: October 31, 2003

Our Reference Number: NDA 21-700

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 December 30, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 31, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-700

Page 2

If you have any questions, please me at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lina Aljuburi

11/6/03 03:47:52 PM

Sent to document room

12/30/03

USER FEE PAYMENT & PDUFA/FDAMA VALIDATION SHEET

Must be completed for ALL original NDAs, efficacy supplements and initial rolling review submissions

21-700 SUPP TYPE & # N000 Division 510 UFID
Applicant Name: Glaxo Smith Kline Drug Name: Avandaryl Tablets

For assistance in filling out this form see the Document Processing Manual for complete instructions and examples.

1. Was a Cover Sheet submitted?

[X] Yes [] No

2. Firm in Arrears?

[] Yes [X] No

3. Bundling Policy Applied Appropriately? Refer to Draft "Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees" http://www.fda.gov/cder/guidance

[X] Yes [] No (explain in comments)

4. Administrative Split? (list all NDA#s and Divisions)

NDA #/Doc Type Div. Fee? (Y/N)

N/A

5. Type 6?

[] Yes [X] No

Type 6 to which other application?

NDA # Supp Type & #

6. Clinical Data Required for Approval? (Check one)

[X] Yes*

[] Yes, by reference to another application

NDA # Supp Type & #

[] No

* Yes if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., adding an adverse reaction, contraindication or warning to the labeling).

7. 505(b)(2) application? (NDA original applications only) Refer to Draft "Guidance for Industry Applications Covered by Section 505(b)(2)" http://www.fda.gov/cder/guidance

[] Yes [X] No [] To be determined

8. Subpart H (Accelerated Approval/Restricted Distribution)?

[] Yes [X] No [] To be determined

9. Exclusion from fees? (Circle the appropriate exclusion. For questions, contact User Fee staff)

List of exclusions:

- 2- No fee - administrative split
4- No fee - 505b2
7- Supplement fee - administrative split
9- No fee Subpart H supplement- confirmatory study
11- No fee Orphan Exception
13- No fee State/Federal exemption from fees

10. Waiver Granted?

[] Yes (letter enclosed) [X] No

Select Waiver Type below: Letter Date:

- [] Small Business [] Barrier-to-Innovation
[] Public Health [] Other (explain)

11. If required, was the appropriate fee paid?

[X] Yes [] No

12. Application Review Priority

[] Priority [X] Standard [] To be determined

13. Fast Track/Rolling Review Presubmission?

[] Yes [X] No

Comments

Signature: [Signature] Date: 12-30-03
PM Signature/Date

This form is the initial data extraction of information for both User Fee payment and PDUFA/FDAMA data elements. The information entered may be subject to change due to communication with the User Fee staff. This form will not reflect those changes. Please return this form to your document room for processing.

CC: original archival file HFD-007

Processor Name & Date

DN 11-04-03

QC Name & Date

BL 11-4-03

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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>

1. APPLICANT'S NAME AND ADDRESS

SB Pharmco Puerto Rico Inc. d/b/a GlaxoSmithKline
Road 172, Km 9.1/Bo. Certenejas
Post Office Box 11975
Cidra, Puerto Rico 00739-1975

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
21-700

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

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:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

NDA 21-071

(APPLICATION NO. CONTAINING THE DATA)

RECEIVED

OCT 31 2003

CDR/CDER

2. TELEPHONE NUMBER (Include Area Code)

(215) 751-3868

3. PRODUCT NAME

Avandaryl [rosiglitazone maleate/glimepiride combination tablets, SB 797620]

6. USER FEE I.D. NUMBER

4613

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

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:

Department of Health and Human Services
Food and Drug Administration
CDER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

Linda Rebar

TITLE

Associate Director
U.S. Regulatory Affairs

DATE

10/31/2003

**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

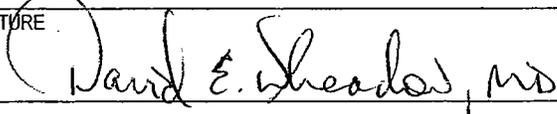
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the 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)). **[Aventis Study HOE 490/4034]**
- (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 Wheadon, MD	TITLE Senior Vice President, US Regulatory Affairs
FIRM / ORGANIZATION GlaxoSmithKline	
SIGNATURE 	DATE 10/31/2003

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

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 2, 2003

TIME: 11:00 am – 12:00 noon

LOCATION: Parklawn Conference Center, Potomac Room

APPLICATION: PIND 66,162, Avandia/Amaryl (rosiglitazone/glimepiride) Tablets

TYPE OF MEETING: pre-NDA

MEETING CHAIR: David Orloff, MD

MEETING RECORDER: Kati Johnson

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

David G. Orloff, MD-Division Director, Division of Metabolic & Endocrine Drug Products (DMEDP)
Joanna Zawadzki, MD-Medical Officer, DMEDP
Hae Young Ahn, PhD-Team Leader, Clinical Pharmacology
Xavier Ysem, PhD-Chemistry Reviewer
Kati Johnson, Chief, Project Management Staff

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

GlaxoSmithKline:

Hubert Chou, M.D.	Director, Metabolic Clinical Development and Medical Affairs, North America
Lisa Porter, M.D.	Director, Metabolic Clinical Development and Medical Affairs, North America
Stuart Dollow, M.D.	Vice President, Full Development Clinical Pharmacology (Metabolic Diseases)
Paul Mudd, Pharm.D.	Principal Clinical Pharmacologist, Clinical Pharmacology Discovery Medicine
Donald Mackenzie, Ph.D.	Director, Pharmaceutical Development
Michael Brennan, Ph.D	Director, Submission Strategy and Support
Justin Geiger	Assistant Director, Global CMC Regulatory Affairs
Clare Kahn, Ph.D.	Vice President, North America Regulatory Affairs
Linda Rebar	Associate Director, North America Regulatory Affairs

Aventis:

Carl Mendel, M.D.	Global Project Team Leader
Chanda Moseley, Ph.D.	Global Regulatory Affairs Liaison
Joseph Scheeren, Ph.D.	Senior Director of Regulatory Affairs
Stephan Schmidt, Ph.D.	Director, Stability and Analytical Services

BACKGROUND:

Rosiglitazone (Avandia, NDA 21-071) and glimepiride are indicated as monotherapy and in combination with other anti-diabetic agents as an adjunct to diet and exercise for the treatment of Type II diabetes.

On March 19, 2003, the firm requested a pre-NDA meeting to discuss their proposed submission of an NDA for a fixed dose tablet formulation. The background package for the meeting was submitted May 6, 2003. The firm anticipates a November 2003 NDA submission.

MEETING OBJECTIVE:

Review and discuss GSK's plans to secure a second line indication for the rosiglitazone/glimepiride combination product.

AGENDA:

The firm proposed specific questions to which they requested a response. The firm's questions are repeated below and followed by the Agency response (**bolded**).

CLINICAL

1. GSK is developing three tablet strengths of the rosiglitazone/glimepiride combination: 4 mg/1 mg; 4 mg/2 mg; and 4 mg/4 mg, initially for second line treatment of type 2 diabetes mellitus. These three fixed-dose combination ratios are in line with the current approved prescribing information of Avandia® (rosiglitazone maleate) and Amaryl® (glimepiride). The proposed combination tablet strengths are consistent with the requirement set forth in 21 CFR 300.50: "the dosage of each component is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drugs". Refer to Section 4 of this briefing package for a discussion of the rationale for the dose selection.
Does the Division agree with our assessment?

Response: It appears acceptable for second line treatment of type 2 diabetes mellitus. A final decision can only be made once the application has been submitted for a comprehensive review.

2. The development plan for the rosiglitazone/glimepiride combination tablet will consist of the following pharmacokinetic studies:
 - an interaction study
 - a bioequivalence study
 - a food effect study
 - a dose-proportionality study

We believe that the pharmacokinetic studies can serve to bridge the proposed combination tablets to the clinical safety and efficacy database supporting the use of rosiglitazone in combination with sulfonylureas existing under the approved NDA 21-071. Further supportive clinical data will be provided as follows: (1) a study (234) of rosiglitazone in combination with glimepiride and (2) studies of rosiglitazone in combination with other sulfonylureas conducted since the initial approval. These additional studies with sulfonylureas corroborate prior conclusions that safety and efficacy are consistent when rosiglitazone is used in combination with a sulfonylurea. Refer to Section 5 of this briefing package for a discussion of the proposed development program.

Is this approach acceptable to the Division for approval of a second line indication?

Response: This approach appears acceptable for approval of a second line indication, pending review of the NDA. It is based primarily on bioequivalence, as the clinical study (BRL 49653/234) evaluated submaximal dose of glimepiride (3 mg), combination therapy of glimepiride 3mg and rosiglitazone placebo, 4 mg, and 8mg rather than the to-be-marketed fixed dose combinations, and no separate rosiglitazone arm.

We believe the program would support the following labeling statement:
Avandaryl is indicated as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes mellitus who are already treated with the combination of rosiglitazone and sulfonylurea, or who are not adequately controlled on a thiazolidinedione or an SU alone.

Does the Agency agree that the above language is reasonable?

Response: The labeling statement will also include a statement that the safety and efficacy of this combination as initial therapy for patients with type 2 diabetes mellitus have not been established. Further comments will be made after review of the NDA submission.

3. Preliminary data from the bioequivalence study are available. This single dose study compared the combination formulation 4 mg rosiglitazone/ 4 mg glimepiride vs rosiglitazone 4 mg + glimepiride 4 mg in the fasted state in healthy volunteers. Bioequivalence of the combination formulation of rosiglitazone 4 mg and glimepiride 4 mg relative to concomitant dosing of rosiglitazone 4 mg and glimepiride 4 mg commercial tablets was demonstrated for AUC of rosiglitazone and glimepiride, and for Cmax of rosiglitazone. Though Cmax of glimepiride was not bioequivalent the observed

minor decrease is not thought to have clinical relevance on the safety or efficacy of the fixed-dose combination. We believe that the results support the approval of the rosiglitazone/glimepiride combination tablets (4 mg/1 mg; 4 mg/2 mg; and 4 mg/4 mg, expressed as rosiglitazone/glimepiride) in line with the strategy presented in question 2 above. Refer to Section 6 of this briefing package for a discussion of the bioequivalence results.

Does the Agency agree with this assessment?

Response: Yes. Since the Cmax of glimepiride is lower in the combination formulation than in the concomitant dosing (0.88, CI 0.76-1.01), there is no safety issue.

- We will be seeking approval of the following tablet strengths (given as rosiglitazone/glimepiride): 4 mg/1 mg; 4 mg/2 mg and 4 mg/4 mg. The active ingredient, rosiglitazone, is identical in all formulations. The active ingredient, glimepiride, increases proportionally across the 3 dose strengths, the tablet weight remaining the same across the dose strengths. All inactive ingredients are proportionally similar to the strength (4 mg/4 mg) on which bioequivalence testing has been conducted with the exceptions of lactose monohydrate () and microcrystalline cellulose (). Refer to Section 8 of this briefing package for details regarding the tablet formulations.

The in vitro dissolution data indicates that the dissolution profiles of all tablet strengths are similar (f2), indicating that the small differences in filler across the dose range dose not affect the release of the active ingredients from the tablets. Refer to Section 8 of this briefing package for details regarding in vitro dissolution of the tablets.

We will be conducting a dose-proportionality study in human volunteers evaluating the 3 tablet strengths (Appendix 2 contains a summary of the dose proportionality protocol). We propose that the combination of clinical dose-proportionality data for glimepiride and the above mentioned in vitro dissolution data for the proposed tablet strengths should be sufficient to obtain approval of all 3 strengths of the combination tablet.

Previously approved clinical data submitted to the Agency for approval of *Amaryl* (glimepiride) shows dose proportionality based upon AUC, but not Cmax:

Comparison	Parameter	Point Estimate	90% CI
1mg:8mg*	AUC	103%	(91%, 113%)
2mg:8mg*	AUC	106%	(93%, 115%)
4mg:8mg*	AUC	103%	(89%, 111%)
1mg:8mg*	Cmax	150%	(130%, 170%)
2mg:8mg*	Cmax	130%	(109%, 148%)
4mg:8mg*	Cmax	114%	(92%, 131%)

* AUC & Cmax values obtained for the 1mg, 2mg, and 4mg tablets were dose-normalized with respect to the 8mg tablet by multiplying results by 8, 4, and 2, respectively

Refer to Appendix 4 of this briefing package for a description of the *Amaryl* dose proportionality study.

Given that AUC is a more pharmacologically relevant parameter than C_{max}, does the Agency agree that demonstration of dose proportionality for glimepiride AUC alone would be acceptable (similar to commercially available *Amaryl*), and would support approval of the three combination tablet strengths?

Response: Yes, pending review of the data.

5. Preliminary data from the interaction study are available. This study was designed to estimate the effect of repeat oral doses of rosiglitazone (8 mg) on the pharmacokinetics of glimepiride (4 mg) and the effect of a single oral dose of glimepiride on the pharmacokinetics of rosiglitazone (8 mg) in healthy subjects. Though minor pharmacokinetic changes were observed, they are not thought to be clinically relevant, and thus support the approval of the rosiglitazone/glimepiride combination tablet in line with the strategy presented in question 2 above. Refer to Section 7 of this briefing package for a discussion of the interaction study results.
Does the Agency agree with this assessment?

Response: Yes

NDA CONTENT/FORMAT

1. We propose to prepare the NDA for the rosiglitazone maleate/glimepiride combination tablets in the Common Technical Document (CTD) format. GSK intends to incorporate certain information (preclinical, clinical and chemistry, manufacturing and controls data) for rosiglitazone maleate and glimepiride by reference to NDA 21-071 and NDA 20-496 respectively. Neither NDA 21-071 nor NDA 20-496 are currently organized or formatted in-the CTD format.
Does the Agency agree with is proposal?

Response: Yes.

2. GSK plans to provide this submission electronically as a CTD (eCTD) and plans to follow the existing guidance (August 2001). GSK has prepared a prototype CTD submission to illustrate the aspects of the transition from traditional NDA format to the CTD format. This should give the review team a good indication as to how they will be able to access key efficacy and safety information. If the Division feels that it would be useful, we would be pleased to present the prototype to the Division in a subsequent meeting.

Does the Agency have any comments regarding the eCTD?

Response: The firm was referred to Ken Edmunds in the Office of Information Technology.

Would the Division find it useful to have a presentation of a prototype CTD in a subsequent meeting?

Response: Not at this time. We will keep this option open once the application has been submitted and assigned for review.

3. The following studies will form the core of the NDA:
- an interaction study
 - a bioequivalence study
 - a food effect study
 - a dose-proportionality study
 - clinical study 234 evaluating rosiglitazone in combination with glimepiride

Reports will also be included for the studies that evaluated rosiglitazone in combination with sulfonylureas other than glimepiride. A number of the clinical studies, including study 234, were conducted outside of the US and therefore not under the US IND.

Case report forms (as electronic images only) for all patients who died during the clinical study or who did not complete the study because of an adverse event will be included for the above-mentioned studies.

Does the Agency agree with the proposal for the submission of case report forms?

Response: Yes. Severe adverse events should be included as narrative summaries.

Does the Agency have any particular concerns about using non-US, non-IND studies to support the safety and efficacy of the rosiglitazone/glimepiride combination products?

Response: No. As noted above, the basis for approval of this fixed combination product will be bioequivalence.

CHEMISTRY, MANUFACTURING, AND CONTROLS

1. Glimepiride specifications - The rosiglitazone maleate /glimepiride combination tablets are formulated with rosiglitazone maleate drug substance as provided for in NDA 21-071, and glimepiride drug substance as provided for in Aventis Pharma's NDA 20-496. The proposed specification for glimepiride is the same drug substance specification approved in NDA 20-496.

Does the Agency have any other items for consideration for the glimepiride drug substance specification?

Response: Drug substance specifications for glimepiride as provided in NDA 20-496 is acceptable.

1 Page(s) Withheld

 ✓ Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-

 4

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

None

Minutes Preparer: Kati Johnson, Chief, Project Management Staff
Chair Concurrence: David Orloff, Division Director

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

/s/

Kati Johnson
6/20/03 05:47:25 AM



PIND 66,162

GlaxoSmithKline
Attention: Ms. Linda Rebar
Associate Director, US Regulatory Affairs
200 North 16th Street
FP-1005
Philadelphia, PA 19102

Dear Ms. Rebar:

Please refer to the meeting between representatives of your firm and FDA on June 2, 2003. The purpose of the meeting was to discuss your plans for development of rosiglitazone maleate/glimepiride combination tablet (SB 797620) for the treatment of patients with Type II diabetes mellitus.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6380.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Chief, Project Management Staff
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of the June 2, 2003 preNDA meeting minutes