CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-700

CHEMISTRY REVIEW(S)

NDA 21-700

Avandaryl™ Tablets

(Rosiglitazone Maleate and Glimepiride Combination Tablets)

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

CMC Review # 3

Xavier Ysern, PhD

ONDQA/ DPA I/ Branch II

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CHEMISTRY REVIEW

Chemistry Review Data Sheet

1. **NDA:** 21-700

2. **Review #:** 3

3. **Review Date:** 22-NOV-2005

4. **Reviewer:** Xavier Ysern, PhD HFD-820

5. **Previous Documents:**

Previous Documents		Document Date
IND 66,162 AmarylAvandia (Glimepiride/Rosiglitazone) Tablet	GlaxoSmithKline	07-NOV-2002

6. **Submission(S) Being Reviewed:**

Submission(s) Reviewed	Document Date
Original	31-OCT-2003
Amendment	24-JUN-2005
Amendment	06-AUG-2004
Amendment	23-SEP-2005
Amendment	07-NOV-2005

7. **Name & Address Of Applicant:**

Name:	SB Pharmco Puerto Rico d/b/a GlaxoSmithKline
Address:	Road 172, Km 9.1/Bo. Certenejas P. O. Box 11975 Cidra, Puerto Rico 00739-1975
Representative:	Linda Rebar GlaxoSmithKline 200 N. 16th Street Philadelphia, PA 19102
Telephone:	(215) 751 4038 / (215) 751 4926 (fax)

8. **Drug Product Name/Code/Type:**

a) Proprietary Name:	Avandaryl™ Tablets
b) Non-Proprietary Name:	Rosiglitazone Maleate and Glimepiride Combination Tablets
c) Code Name:	SB 797620
d) Chem. Type/Submission Priority:	· Chem. Type: 4 · Submission Priority: S

9. **Legal Basis For Submission:** 505 (b)(1)

10. **Pharmacol. Category:** Hypoglycemic agent. Treatment of Type 2 diabetes mellitus as an adjunct to diet and exercise

11. **Dosage Form:** Tablet

12. **Strength/Potency:** 4-mg/1-mg, 4-mg/2-mg, and 4-mg/4-mg

13. **Route Of Administration:** Oral

14. Rx/OTC Dispensed: Rx

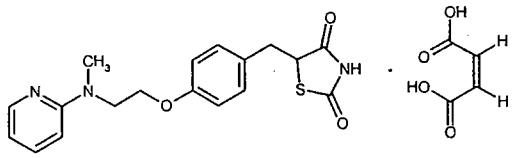
15. Spots (Special Products On-Line Tracking System): Not a SPOTS product

16. Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:

Rosiglitazone maleate

$C_{18}H_{19}N_3O_4S \cdot C_4H_4O_4$

MW = 357.4 + 116.1 = 473.5



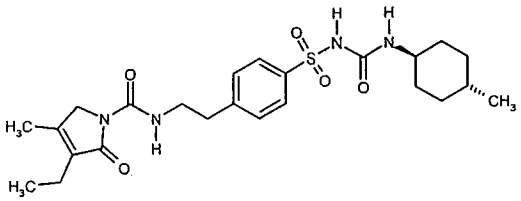
(±)-5[[4-[2-Methyl-2-(pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione (*Z*)-2-butenedioate (1:1)

Glimepiride

$C_{24}H_{34}N_4O_5S$

MW = 490.62

CAS 93479-97-1



1*H*-Pyrrole-1-carboxamide,3-ethyl-2,5-dihydro-4-methyl-N-[2-[4-[[[[(4-methylcyclohexyl)amino]carbonyl]amino] sulfonyl]phenyl]ethyl]-2-oxo, *trans*-

17. Related/Supporting Documents:

A. DMFs:

DMF #	LOA date	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
Type III							
[redacted]	07-JUN-2002	[redacted]	[redacted]	4	Adequate		
	03-JUL-2002			4	Adequate		
	06-JUN-2002			4	Adequate		
	30-JUL-2003			4	Adequate		
	11-JUN-2002			4	Adequate		
	10-JUN-2002			4	Adequate		
	12-JUN-2004			4	Adequate		
	03-SEP-2002			4	Adequate		
Type IV							
[redacted]	01-JUL-2003	[redacted]	[redacted]	4	Adequate		
	01-JUL-2003			4	Adequate		
	01-JUL-2003			4	Adequate		

(1) Action codes for DMF Table: 1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

Document	Application #	Description
NDA	21-071	Avandia® (rosiglitazone maleate) Tablet
NDA	21-410	Avandamet™ (rosiglitazone maleate and metformin hydrochloride) Tablet
IND	43,468	Rosiglitazone

18. Status:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	--	--	--
EES	Acceptable	22-NOV-2005	District Office Recommendation
Pharm/Tox	--	--	--
Biopharm	--	--	--
ODS/DMETS	Pending (Avandaryl tradename)		
Methods Validation	Revalidation of test methods by Agency laboratories deemed not necessary		Xavier Ysern, PhD
EA	Acceptable		Xavier Ysern, PhD
Microbiology	--	--	--

CHEMISTRY REVIEW

Chemistry Review Data Sheet

The Chemistry Review for NDA 21-700

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA can be approved.

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

There are no CMC Phase IV Commitments.

II. Summary of Chemistry Assessments

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

1. Drug Substances See CMC Reviews #1 and 2

2. Drug Product See CMC Reviews #1 and 2

B. Description of How the Drug Product is Intended to be Used See CMC Review #1 and 2

C. Basis for Approvability or Not-Approval Recommendation

This NDA **can be approved with respect to Chemistry, Manufacturing, and Controls (CMC).** All pending issues have been resolved (See attached EER Summary Report dated 22-NOV-2005).

III. Administrative

A. Reviewer's Signature

See electronic signature page.

B. Endorsement Block

Chemist Name:	Xavier Ysern, PhD/22-NOV-2005
ONDQA/DPA I/Branch I Branch Chief	Blair Fraser, PhD Signed by Suong Tran, PhD

C. CC Block

Rik Lostritto, PhD	ONDQA/DPA I/Division Director
Project Manager:	Lina Aljuburi, PharmD (HFD-510)

3 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-1

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

/s/

Xavier Ysern
11/22/2005 02:02:03 PM
CHEMIST

Suong Tran
11/22/2005 02:22:32 PM
CHEMIST
For Blair Fraser

Richard Lostritto
11/23/2005 12:46:54 PM
CHEMIST

NDA 21-700

Avandaryl™ Tablets

(Rosiglitazone Maleate and Glimepiride Combination Tablets)

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

CMC Review # 2

Xavier Ysern, PhD

HFD-510

Table of Contents

CHEMISTRY REVIEW

Chemistry Review Data Sheet

1. **NDA:** 21-700

2. **Review #:** 2

3. **Review Date:** 08-JUN-2005

4. **Reviewer:** Xavier Ysern, PhD HFD-820

5. **Previous Documents:**

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IND 66,162 AmarylAvandia (Glimepiride/Rosiglitazone) Tablet	GlaxoSmithKline	07-NOV-2002

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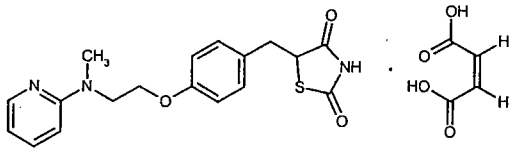

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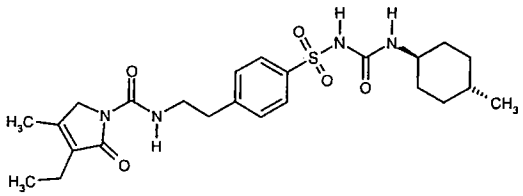

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	12-JUN-2004			4	Adequate		
	03-SEP-2002			4	Adequate		
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	01-JUL-2003			4	Adequate		
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Biopharm	--	--	--
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EA	Acceptable		Xavier Ysern, PhD
Microbiology	--	--	--

Chemistry Review Data Sheet

The Chemistry Review for NDA 21-700

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA can be approved.

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

There are no CMC Phase IV Commitments.

II. Summary of Chemistry Assessments

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

1. Drug Substances

The drug product Avandaryl™ Tablets is a combination drug product containing two active components: rosiglitazone maleate and glipizide. Both drug substances have been described under approved NDAs. Information on the drug substance rosiglitazone maleate is included by cross-reference to NDA 21-071, Avandia® (rosiglitazone maleate) Tablets approved on May 25, 1999. Information pertinent to the drug substance glimepiride is included by cross-reference to Aventis Pharmaceuticals' NDA 20-496, Amaryl® (glimepiride) Tablets, approved on November 30, 1995. Although both rosiglitazone and glymepiride are hypoglycemic agents used for the treatment of patients with Type 2 diabetes mellitus, they differ in both chemical class and mechanism of action.

Rosiglitazone ((±)-5[[4-[2-Methyl-2-(pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione (*Z*)-2-butenedioate (1:1)), a thiazolidinedione derivative, is a highly selective and potent agonist for the peroxisome proliferator -activated receptor- gamma (PPARγ). Activation of PPARγ nuclear receptors regulates the transcription of insulin-related genes involved in the control of glucose production, transport, and utilization. Rosiglitazone's antidiabetic activity is mediated by increased sensitivity to insulin's action in the liver, muscle and adipose tissues. In humans, PPARγ receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle and liver. Rosiglitazone (code name BRL 49653), which belongs to the glitazone class, is synthesized as a racemate.

[redacted]

So, administration of either enantiomer would not provide any advantage over administration of the racemate. Rosiglitazone maleate is a white to off-white solid with a melting point range of 122° to 123°C. The pKa values of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range.

Glimepiride (1*H*-Pyrrole-1-carboxamide, 3-ethyl-2,5-dihydro-4-methyl-N-[2-[4-[[[[(4methylcyclohexyl) amino]carbonyl]amino]sulfonyl]phenyl]ethyl]-2-oxo, *trans*-) is an oral glucose-lowering drug of the sulfonylurea class.

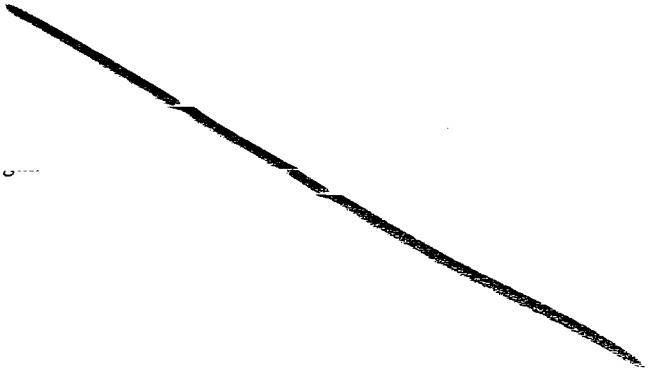
[redacted]

. Glimepiride is a white to yellowish-white, crystalline, odorless to practically odorless powder. Glimepiride is practically insoluble in water.

Chemistry Review Data Sheet

2. Drug Product

Avandaryl (Rosiglitazone Maleate and Glimepiride) Combination Tablets are designed to provide fast release of the two active ingredients, rosiglitazone and glimepiride. The release profiles of those active components from Avandaryl™ Tablets are similar to that for rosiglitazone in Avandia® Tablets and for glimepiride in Amaryl® Tablets. The tablets contain the two active components rosiglitazone maleate and glimepiride, plus the following inactive ingredients: Lactose monohydarate, microcrystalline cellulose, sodium starch glycolate, hypromellose (HPMC) 2910, polyethylene glycol, magnesium stearate, titanium dioxide, and one or more of the following: Yellow, red, or black iron. [redacted]. Three tablet strengths, 4-mg/1-mg, 4-mg/2-mg, and 4-mg/4-mg, are proposed for Avandaryl (rosiglitazone/glimepiride) Tablets. Although the three different film coated tablet strengths have the same rounded triangular shape and weight, they are easily distinguished by color and debossed strength markings.



Drug product specifications are consistent with those for Avandia and Amaryl Tablets. Identification of the active components, their quantification and purity determinations are carried out by validated HPLC methodologies. Active components content are within ± 10 % of labeled amounts, a common requirement for oral dosage forms. Drug-related impurities from rosiglitzone can not exceed [redacted] and their total limited to NMT [redacted] For drug-related impurities derived from glimepiride the acceptance criterion is NMT [redacted] for glimepiride sulfonamide, any unspecified impurity NMT [redacted] and the total impurities can not exceed [redacted] Although Avandia and Amaryl tablet dissolution conditions differ, for Avandaryl Tablets the applicant developed a dissolution method able to determine the dissolution rate of rosiglitazone and glimepiride simultaneously from the combination tablet.

Tablets are packaged into [redacted] bottles [redacted] Fill counts for the bottles include 30, [redacted] tablets. [redacted] The stability data for Avandaryl Tablets is derived from six pilot scale batches packaged in the proposed commercial packaging configurations. [redacted] Currently, stability data up to [redacted] at controlled room temperature and [redacted] under stress conditions (40 °C/75 % RH) has been provided. All available test results are within specifications, [redacted], no significant changes were observed. Based on the available stability data, cumulative stability data on Avandia and Amaryl Tablets, and statistically calculated/extrapolated shelf-life estimates, an initial shelf-life of 24 months is granted for the [redacted] bottle packaging configurations [redacted]

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

Avandaryl Tablets are designed to provide an oral administration of a fix dose of 4 mg rosiglitazone with variable doses of glimepiride (1, 2, or 4 mg) in a single tablet. Avandaryl is indicated 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 [redacted] sulfonylurea alone. Avandaryl should be given once daily with a meal. As any antidiabetic therapy, the dosage of Avandaryl should be individualized on the basis of effectiveness and tolerability. 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. When switching from combination therapy of rosiglitazone plus glimepiride as separate tablets, the usual starting dose of Avandaryl 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. Although the concomitant administration of Avandia (rosiglitazone maleate) Tablets and Amaryl (glimepiride) Tablets could provide the same dosage that Avandaryl, the use of Avandaryl Tablets simplify administration and facilitates patient compliance.

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable from a CMC viewpoint. This recommendation is based upon evaluation of the CMC information provided by the applicant. The only pending issue, acceptable recommendation by the Office of Compliance, has been resolved (see attached EER Summary Report dated 08-JUN-2005).

III. Administrative

A. Reviewer's Signature

See electronic signature page.

B. Endorsement Block

Chemist Name:	Xavier Ysern, PhD/08-JUN-2005
Chemistry Team Leader:	Stephen Moore, PhD
Project Manager:	Lina Aljuburi, PharmD

C. CC Block

Attached:

CHEMISTRY REVIEW

Chemistry Review Data Sheet

09-JUN-2005 FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 21700/000
Org Code : 510
Priority : 4S

Sponsor: GLAXOSMITHKLINE
7929
PHILADELPHIA, PA 191017929

Stamp Date : 31-OCT-2003
PDUFA Date : 31-AUG-2004
Action Goal :
District Goal: 02-JUL-2004

Brand Name : AVANDARYL(ROSIGLITAZONE MALEATE/GLIMEPIR
Estab. Name:
Generic Name: ROSIGLITAZONE MALEATE/GLIMEPIRIDE COMBIN
Dosage Form: (TABLET)
Strength : 4-/1-, 4-/2-& 4-MG/4-MG

FDA Contacts:			
	L. ALJUBURI	Project Manager (HFD-510)	301-827-6414
	X. YSERN	Review Chemist (HFD-510)	301-827-6420
	S. MOORE	Team Leader (HFD-510)	301-827-6401

Overall Recommendation: ACCEPTABLE on 08-JUN-2005by C. CRUZ (HFD-323) 301-827-9013
WITHHOLD on 17-AUG-2004by R. WOODS (HFD-322) 301-827-9011

Establishment : CFN : 2650115 FEI : 2650115
SMITHKLINE BEECHAM PHARMACEUTICALS CO
RD 172 KM 9.1 BO CERTENEJAS
CIDRA, PR 00739

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile : TCM OAI Status: NONE
Last Milestone : OC RECOMMENDATION
Milestone Date: 08-JUN-05
Decision : ACCEPTABLE
Reason : DEFIC. NOT SUPPORTED BY CDER

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

/s/

Xavier Ysern
6/9/05 10:52:04 AM
CHEMIST

Stephen Moore
6/9/05 11:25:40 AM
CHEMIST

NDA 21-700

Avandaryl™ Tablets

(Rosiglitazone Maleate and Glimepiride Combination Tablets)

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

Xavier Ysern, PhD

HFD-510

Table of Contents

Chemistry Review Data Sheet

1. **NDA:** 21-700

2. **Review #:** 1

3. **Review Date:** 10-JUN-2004

4. **Reviewer:** Xavier Ysern, PhD HFD-820

5. **Previous Documents:**

Previous Documents		Document Date
IND 66,162 AmarylAvandia (Glimepiride/Rosiglitazone) Tablet	GlaxoSmithKline	07-NOV-2002

6. **Submission(S) Being Reviewed**:

Submission(s) Reviewed	Document Date
Original	31-OCT-2003
Amendment	29-JAN-2004
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Amendment	13-MAY-2004
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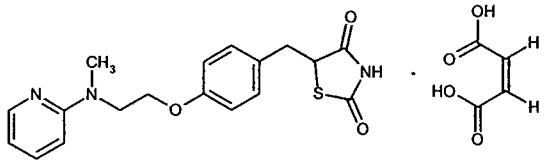

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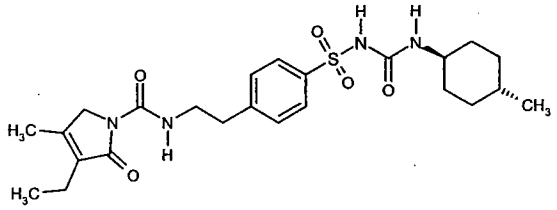

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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

Document	Application #	Description
NDA	21-071	Avandia® (rosiglitazone maleate) Tablet
NDA	21-410	Avandamet™ (rosiglitazone maleate and metformin hydrochloride) Tablet
IND	43,468	Rosiglitazone

18. Status:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	--	--	--
EES	Pending		
Pharm/Tox	--	--	--
Biopharm	--	--	--
ODS/DMETS	Pending (Avandaryl tradename)		
Methods Validation	Pending		
EA	Acceptable		Xavier Ysern, PhD
Microbiology	--	--	--

The Chemistry Review for NDA 21-700

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is APPROVABLE pending satisfactory cGMP inspection of facility used to manufacture the drug product. Currently, the status of this facility is WITHOLD pending regulatory action - Warning Letter (see page 52). A statement should be included in the SB Pharmco PR action letter regarding the drug product expiry dates (see list of deficiencies).

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

There are no CMC Phase IV Commitments.

II. Summary of Chemistry Assessments

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

1. Drug Substances

The drug product Avandaryl™ Tablets is a combination drug product containing two active components: rosiglitazone maleate and glipizide. Both drug substances have been described under approved NDAs. Information on the drug substance rosiglitazone maleate is included by cross-reference to NDA 21-071, Avandia® (rosiglitazone maleate) Tablets approved on May 25, 1999. Information pertinent to the drug substance glimepiride is included by cross-reference to Aventis Pharmaceuticals' NDA 20-496, Amaryl® (glimepiride) Tablets, approved on November 30, 1995. Although both rosiglitazone and glymepiride are hypoglycemic agents used for the treatment of patients with Type 2 diabetes mellitus, they differ in both chemical class and mechanism of action.

Rosiglitazone ((±)-5[[4-[2-Methyl-2-(pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione (*Z*)-2-butenedioate (1:1)), a thiazolidinedione derivative, is a highly selective and potent agonist for the peroxisome proliferator -activated receptor- gamma (PPARγ). Activation of PPARγ nuclear receptors regulates the transcription of insulin-related genes involved in the control of glucose production, transport, and utilization. Rosiglitazone's antidiabetic activity is mediated by increased sensitivity to insulin's action in the liver, muscle and adipose tissues. In humans, PPARγ receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle and liver. Rosiglitazone (code name BRL 49653), which belongs to the glitazone class, is synthesized as a racemate.

[redacted] So, administration of either enantiomer would not provide any advantage over administration of the racemate. Rosiglitazone maleate is a white to off-white solid with a melting point range of 122° to 123°C. The pKa values of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range.

Glimepiride (1*H*-Pyrrole-1-carboxamide, 3-ethyl-2,5-dihydro-4-methyl-N-[2-[4-[[[[(4methylcyclohexyl) amino]carbonyl]amino]sulfonyl]phenyl]ethyl]-2-oxo, *trans*-) is an oral glucose-lowering drug of the sulfonylurea class.

[redacted] Glimepiride is a white to yellowish-white, crystalline, odorless to practically odorless powder. Glimepiride is practically insoluble in water.

2. Drug Product

Avandaryl (Rosiglitazone Maleate and Glimepiride) Combination Tablets are designed to provide fast release of the two active ingredients, rosiglitazone and glimepiride. The release profiles of those active components from Avandaryl™ Tablets are similar to that for rosiglitazone in Avandia® Tablets and for glimepiride in Amaryl® Tablets. The tablets contain the two active components rosiglitazone maleate and glimepiride, plus the following inactive ingredients: Lactose monohydarate, microcrystalline cellulose, sodium starch glycolate, hypromellose (HPMC) 2910, polyethylene glycol, magnesium stearate, titanium dioxide, and one or more of the following: Yellow, red, or black iron. [redacted] Three tablet strengths, 4-mg/1-mg, 4-mg/2-mg, and 4-mg/4-mg, are proposed for Avandaryl (rosiglitazone/glimepiride) Tablets. Although the three different film coated tablet strengths have the same rounded triangular shape and weight, they are easily distinguished by color and debossed strength markings.

[redacted]

Drug product specifications are consistent with those for Avandia and Amaryl Tablets. Identification of the active components, their quantification and purity determinations are carried out by validated HPLC methodologies. Active components content are within ± 10 % of labeled amounts, a common requirement for oral dosage forms. Drug-related impurities from rosiglitzone can not exceed [redacted] and their total limited to NMT [redacted]. For drug-related impurities derived from glimepiride the acceptance criterion is NMT [redacted] for glimepiride sulfonamide, any unspecified impurity NMT [redacted] and the total impurities can not exceed [redacted] Although Avandia and Amaryl tablet dissolution conditions differ, for Avandaryl Tablets the applicant developed a dissolution method able to determine the dissolution rate of rosiglitazone and glimepiride simultaneously from the combination tablet.

Tablets are packaged into [redacted] bottles [redacted] Fill counts for the bottles include 30, [redacted] tablets. [redacted] . The stability data for Avandaryl Tablets is derived from six pilot scale batches packaged in the proposed commercial packaging configurations. [redacted] Currently, stability data up to [redacted] at controlled room temperature and [redacted] under stress conditions (40 °C/75 % RH) has been provided. All available test results are within specifications, [redacted] no significant changes were observed. Based on the available stability data, cumulative stability data on Avandia and Amaryl Tablets, and statistically calculated/extrapolated shelf-life estimates, an initial shelf-life of 24 months is granted for the [redacted] bottle packaging configurations [redacted]

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

Avandaryl Tablets are designed to provide an oral administration of a fix dose of 4 mg rosiglitazone with variable doses of glimepiride (1, 2, or 4 mg) in a single tablet. Avandaryl is indicated 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 [redacted] sulfonylurea alone. Avandaryl should be given once daily with a meal. As any antidiabetic therapy, the dosage of Avandaryl should be individualized on the basis of effectiveness and tolerability. 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. When switching from combination therapy of rosiglitazone plus glimepiride as separate tablets, the usual starting dose of Avandaryl 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. Although the concomitant administration of Avandia (rosiglitazone maleate) Tablets and Amayl (glimepiride) Tablets could provide the same dosage that Avandaryl, the use of Avandary Tablets simplify administration and facilitates patient compliance.

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable from a CMC viewpoint. This recommendation is based upon evaluation of the CMC information provided by the applicant. A final recommendation by the Office of Compliance is pending.

III. Administrative

A. Reviewer's Signature

See electronic signature page.

B. Endorsement Block

Chemist Name:	Xavier Ysern, PhD/28-MAY-2004
Chemistry Team Leader:	Stephen Moore, PhD
Project Manager:	Lina Aljuburi, PharmD

C. CC Block

50 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 2

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

/s/

Xavier Ysern
7/8/04 04:34:35 PM
CHEMIST

Stephen Moore
7/8/04 05:36:29 PM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21700/000	Action Goal:	
Stamp:	31-OCT-2003	District Goal:	02-JUL-2004
Regulatory Due:	26-NOV-2005	Brand Name:	AVANDARYL(ROSIGLI AZONE
Applicant:	GLAXOSMITHKLINE	Estab. Name:	MALEATE/GLIMEPIR
	7929	Generic Name:	ROSIGLITAZONE
	PHILADELPHIA, PA 191017929		MALEATE/GLIMEPIRI E
Priority:	4S		COMBIN
Org Code:	510	Dosage Form:	(TABLET)
		Strength:	4-/1-, 4-/2-& 4-M /4-MG

Application Comment: MANUFACTURE, PRIMARY AND SECONDARY PACKAGING OF BATCHES, QUALITY CONTROL AND APPROVAL FOR RELEASE, AND STABILITY TESTING ARRIED OUT AT THIS FACILITY (on 24-DEC-2003 by X. YSERN () 301-96-2410)

FDA Contacts:	L. ALJUBURI	301-796-1168	, Project anager
	X. YSERN	301-796-2410	, Review C emist
	S. MOORE	301-796-1718	, Team Lea er

Overall Recommendation: ACCEPTABLE on 17-NOV-2005by S. ADAMS (HFD-322)301-27-9051

WITHHOLD on 17-AUG-2004by R. WOODS (HFD-322)301-27-9011

Establishment: [redacted]

DMF No: AADA:

Responsibilities: [redacted]

P File: CSN OAI Status: NONE

Estab. Comment: [redacted]
. DS

4-JUN-

2005 by X. YSERN () 301-796-2410)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	14-JUN-2005				YSERNX
SUBMITTED TO DO	14-JUN-2005	PS			DABROGIOJ
DO RECOMMENDATION	17-JUN-2005			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	17-JUN-2005			ACCEPTABLE DISTRICT RECOMMENDATION	\MSS

Establishment: CFN 9610176 FEI 1000170338
GLAXOSMITHKLINE
CURRAGHBINNY
CARRIGALINE, CO. CORK, , EI

DMF No: AADA:

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

R ponsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

Profile: CSN OAI Status: NONE

Estab. Comment: [redacted] DR G

O

PROFILE. (on 14-JUN-2005 by X. YSERN () 301-796-2410)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	C eator
SUBMITTED TO OC	14-JUN-2005				YSERNX
SUBMITTED TO DO	14-JUN-2005	PS			DA BROGIOJ
IGNED INSPECTION T	17-JUN-2005	PS			AMSS
INSPECTION SCHEDULED	26-AUG-2005		01-SEP-2005		IRIVERA
INSPECTION PERFORMED	31-AUG-2005		31-AUG-2005		JOE .QUITAN

This Pre-approval and GMP inspection of an Active Pharmaceutical Ingredient manuf cturer

was conducted in response to an EES assignment from CDER requesting inspectional overage

for NDA 21-700, Rosiglitazone Maleate API. The inspection was performed in accor ance to

CP 7356.002, Drug Process Inspection and CP 7346.832, Pre-Approval Inspection/Met od

Validations under FACTS assignment# 3055959. Profile class CSN was covered.

According to the firm, the NDA being submitted is for a new combination product t blet of

iglitazone Maleate with Glimiperide indicated for Type II Diabetes. Rosiglit zo e

Maleate API is used in other currently approved drug products. The manufacturing process

of Rosiglitazone at this facility is the same regardless of its intended drug pro uct.

The previous inspection of [redacted] was a PAI. That inspection resulted in a 3-item FDA-483

for 1)No data to support assigned dating period of working reference standards

2. Equivalency study for analytical testing was deficient in that it did not accou t for

additional testing when detectable levels for impurities were at trace or non-det ctable

levels 3) No documentation to demonstrate that reconciliation was performed durin

labeling operation of intermediates. Corrections to the previous observations we e

verified during this inspection.

This inspection covered the following systems: Quality, Facilities and Equipment,

Production, Materials and Laboratory. There were no significant observations not d

during this inspection and an FDA-483 was not issued.

RECOMMENDATION ADAMSS	17-NOV-2005	ACCEPTABLE
		INSPECTION
OC RECOMMENDATION ADAMSS	17-NOV-2005	ACCEPTABLE
		DISTRICT RECOMMENDATION

Establishment: CFN 2650115 FEI 2650115

SMITHKLINE BEECHAM PHARMACEUTICALS CO

RD 172 KM 9.1 BO CERTENEJAS

CIDRA, PR 00739

DMF No: AADA:

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

Profile: TCM OAI Status: NONE

Estab. Comment: MANUFACTURE, PRIMARY AND SECONDARY PACKAGING OF BATCHES, QUALITY CONTROL AND APPROVAL FOR RELEASE, AND STABILITY TESTING CARRIED OUT AT THIS FACILITY (on 24-DEC-2003 by X. YSERN () 301-796-2410)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	24-DEC-2003				YSERNX
SUBMITTED TO DO	29-DEC-2003	10D			DA BROGIOJ
R RECEIVED BY OC	17-JAN-2004				DSR
DO RECOMMENDATION	22-JAN-2004				IAYALA
LTR					
OC RECOMMENDATION	17-AUG-2004				WOODSR

DISTRICT RECOMMENDATION

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Withheld Track Number: Chemistry- 3