CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-410

CHEMISTRY REVIEW(S)

CDER CHEMISTRY REVIEW CDER

NDA 21-410

Avandamet® Tablets
Rosiglitazone Maleate and Metformin Hydrochloride Tablets

GlaxoSmithKline
(formerly SmithKline Beecham Corporation)

Xavier Ysern, PhD

Division of Metabolism and Endocrine Drug Products HFD-510

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-410

2. REVIEW # 2

3. REVIEW DATE: 10-OCT-2002

4. REVIEWER: Xavier Ysern

5. PREVIOUS DOCUMENTS:

Document(s)	Document Date
IND [redacted]	07-MAR-2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	29-NOV-2001
Amendment	03-DEC-2001
	15-FEB-2002
	17-APR-2002
	24-APR-2002
	20-JUN-2002
	23-AUG-2002
	02-OCT-2002

1. NAME & ADDRESS OF APPLICANT:

Name:	GlaxoSmithKline (formerly SmithKline Beecham Corporation)
Address:	200 N. 16th Street
	Philadelphia, PA 19102
Representative:	Sharon W. Shapowal, R.Ph., Director US Regulatory Affairs
Telephone:	215 751 3434

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Avandamet
b) Non-Proprietary Name (USAN):	rosiglitazone maleate and metformin hydrochloride
c) Code Name:	SB-712753
d) Chem. Type/Submission Priority:	
▪ Chem. Type:	Type 4
▪ Submission Priority:	S

9. LEGAL BASIS FOR SUBMISSION: Not Applicable

10. PHARMACOLOGICAL CATEGORY: Proposed for the treatment of Type 2 diabetes mellitus as an adjunct to diet and exercise

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 1-mg/500-mg, 2-mg/500-mg, and 4-mg/500-mg

Chemistry Review Data Sheet

13. ROUTE OF ADMINISTRATION: Oral

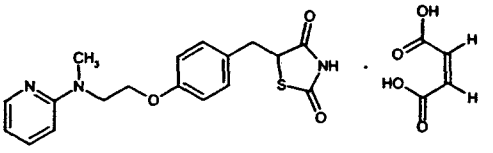
14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note29]: Not a SPOTS product

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

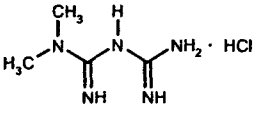
Rosiglitazone maleate

$C_{18}H_{19}N_3O_3S \cdot C_4H_4O_4$
MW = 357.4 + 116.1 = 473.5



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

Metformin Hydrochloride



$C_4H_{11}N_5 \cdot HCl$
MW = 129.17 + 36.46 = 165.63
CAS 657-25-9 (base) 1115-70-4 (hydrochloride)
N,N-Dimethylimidodicarbonimidic diamine monohydrochloride or *N,N*-Dimethylbiguanide HCl

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
				1	Adequate	12-MAR-2001	ANDA 75-975
				1	Adequate	09-APR-2002 09-APR-2002 09-APR-2002	
				4	Adequate		
				3	Adequate	01-APR-1999	
				3	Adequate	08-AUG-2001	
				4	Adequate		
				4	Adequate		
				3	Adequate	07-SEP-2001	DMF Strike Force Reviews
				3	Adequate	12-SEP-2000 18-SEP-2000 22-SEP-2000	
				4	Adequate		GRAS material Not in contact with the DP

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
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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)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-071	Rosiglitazone maleate

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	10-OCT-2002	Office of Compliance
Biopharm	Dissolution Specification. Acceptable.	30-AUG-2002	Stephen Johnson, PhD HFD-870
ODC/DMETS LNC	*Does **not** recommend the use of proprietary name Avandamet*	11-APR-2002	Hye-Joo Kim, RPh HFD-420
Methods Validation	Drug product Assay (rosiglitazone content and Metformin HCl content) and Degradation (Rosiglitazone related and metformin related) methods will be sent for re-validation by Agency laboratories		
EA	The use of Avandamet tablets would not pose a threat to the environment	24-MAY-2002	Xavier Ysern, PhD HFD-820
Microbiology	N/A		

APPEARS THIS WAY
ON ORIGINAL

Executive Summary Section

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is **can be approved.**

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

None.

II. Summary of Chemistry Assessments

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

The **drug product, Avandamet Tablets** is a combination product of two active components, rosiglitazone and metformin. These two active components are antihyperglycemic agents that differ in both chemical class and mode of action. Rosiglitazone, a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPARγ), is a member of the thiazolidinedione class, and Metformin belongs to the biguanide class. Their mechanism of action is well understood, thiazolidinediones are insulin sensitizing agents that act primary by enhancing peripheral glucose utilization, whereas biguanides act primarily by decreasing endogenous hepatic output of glucose by inhibition of gluconeogenesis. Due to their complementary mechanisms of action, concurrent administration of rosiglitazone (Avandia (rosiglitazone) tablets) and metformin (Glucophage or generic metformin hydrochloride tablets) is frequently prescribed. The combination drug product will facilitate patient compliance.

Rosiglitazone, a thiazolidinedione, has one sterocarbon and it is synthesized as a racemate. In solution the two enantiomers are rapidly interconverted and rendered functionally indistinguishable. [redacted] . Rosiglitazone maleate is a white to off-white solid, melting point 122 – 123 °C, pKa values of 6.1 According to the Biopharmaceutics classification system (BCS) rosiglitazone is a class 2 (low solubility-high permeability) drug.

Metformin, a tautomeric compound, is a low molecular biguanide synthesized in [redacted] Metformin hydrochloride is a white to off-white crystalline compound. The pKa of metformin is 12.4. Metformin is a class 3 (high solubility-low permeability) BCS drug.

The two drug substances have the following in common: (1) both are synthesized as salts to improve their stability, (2) their quality is controlled by specifications which are consistent with their respective approved drug substances, rosiglitazone maleate and metformin hydrochloride, (3) particle size, pertinent to manufacture and quality of the drug product, is part of their specifications, (4) in aqueous solution their stability decreases at high pH values, and (5) no evidence of polymorphism.

The tablet **formulation** was developed to provide fast release of the active ingredients. Three different strengths, **1-mg/500-mg, 2-mg/500-mg and 4-mg/500-mg** (rosiglitazone/metformin hydrochloride weight content), are proposed. Drug product manufacture is simplified by [redacted] . A rosiglitazone [redacted] can be mixed with different proportions of an already prepared metformin [redacted] e and [redacted] to give after [redacted] tablets of a desired strength. Although all core tablets have similar weight, size and shape. The three different strengths are easily distinguished by their color coating. The specification criteria of the combination product are consistent with those for Avandia® (rosiglitazone) tablets and for approved metformin tablets.

Avandamet Tablets are **packaged** in bottles and in blister packages. The drug product is commercially available in 60 cc and 100 cc white high-density polyethylene (HDPE) bottles containing 60 and 100 tablets, respectively. Although the lower count is secured with child resistant white polypropylene caps, the 100 tablet count is secured by using a conventional continuous thread cap. Courtesy samples are distributed in [redacted] blister packs. In addition to the mentioned packaging configuration **stability** studies were also carried out in tablets packaged in HDPE bottles of higher container and counts. The results of the stability studies show that the dosage form is compatible with the packaging materials and reconfirm the expected stability of rosiglitazone maleate and metformin hydrochloride in solid oral tablet formulations.

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

Avandamet Tablets is intended to be used orally as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Dosage is based on effectiveness and tolerability, and should not exceed the maximum recommended daily dose of 8 mg/2000 mg. Divided doses with gradual dose escalation would allow the determination of the minimum effective dose. Although there are no food effects (before/with/after meals), Avandamet® tablets should be given with meals to reduce gastrointestinal effects largely due to metformin. The usual starting dose is 2 mg/500 mg to 4 mg/500 mg twice daily. For patients inadequately controlled on metformin monotherapy, the usual starting dose of Avandamet is 4 mg rosiglitazone (total daily dose) plus the dose of metformin already being taken. For patients inadequately controlled on rosiglitazone monotherapy the usual starting dose of Avandamet is 1000 mg of metformin (total daily dose) plus the dose of metformin already being taken.

Avandamet tablets should be stored at controlled room temperature. Based on the available stability data and statistical analysis, at the recommended storage condition, the granted expiration dating is 18 months.

C. Basis for Approvability or Not-Approval Recommendation

All pending issues have been resolved. All manufacturing facilities are have been found acceptable and CMC labeling issues resolved. Based on the evaluation of the information provided in the submission this application can be approved from the Chemistry, Manufacturing and Control (CMC) standpoint.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-510/	Review Chemist	Xavier Ysern	
	Chemistry Team Leader	Stephen Moore	
	Project Manager	Jena Weber	/ 10-OCT-2002

C. CC Block

HFD-820/	NDCDII Director	Eric Duffy
	NDCDII Deputy Director	Duu Gong Wu

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

1 page

10-OCT-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21410/000
Priority: 4S
Org Code: 510
Stamp: 29-NOV-2001 Regulatory Due: 10-OCT-2002
Action Goal:
District Goal: 11-AUG-2002
Applicant: GLAXOSMITHKLINE
5 MOORE DR
RESEARCH TRIANGLE PARK, NC 27
Brand Name: ROSIGLITAZONE MALEATE/METFORMIN HCL TAB
Established Name:
Generic Name: ROSIGLITAZONE MALEATE/METFORMIN HCL TAB
Dosage Form: TAB (TABLET)
Strength: 1/500, 2/500 & 4/500 MG

FDA Contacts:
S. MOORE (HFD-510) 301-827-6430 , Project Manager
X. YSERN (HFD-510) 301-827-6420 , Review Chemist
J. WEBER (HFD-510) 301-827-6422 , Team Leader

Overall Recommendation:

Establishment: [redacted]
DMF No:
AADA No:

Profile: CSN
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 25-JUN-2002
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: [redacted]

Establishment: 9610411
GLAXO OPERATIONS UK LTD

WARE, HERTFORDSHIRE, UK
DMF No:
AADA No:

Profile: CTL
OAI Status: NONE
Last Milestone: INSPECTION PERFORMED
Milestone Date: 19-SEP-2002
Responsibilities: FINISHED DOSAGE STABILITY TESTER

Establishment: 9610176
GLAXOSMITHKLINE
CURRAGHBINNY
COUNTY CORK, , EI
DMF No:
AADA No:

Profile: CSN
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-OCT-2002
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

10-OCT-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

DRUG SUBSTANCE STABILITY TESTER

Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: 2650232
SB PHARMCO PUERTO RICO INC
RD 172 KM 9.1 BO CERTENEJAS
CIDRA, PR 007391975

DMF No:
AADA No:

Profile: TCM
OAI Status: POTENTIAL OAI
Last Milestone: OC RECOMMENDATION
Milestone Date: 10-OCT-2002
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities:
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

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ON ORIGINAL

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

/s/

Xavier Ysern
10/10/02 02:42:18 PM
CHEMIST

Stephen Moore
10/10/02 02:48:25 PM
CHEMIST

CDER CHEMISTRY REVIEW CDER

NDA 21-410

Avandamet® Tablets
Rosiglitazone Maleate and Metformin Hydrochloride Tablets

GlaxoSmithKline
(formerly SmithKline Beecham Corporation)

Xavier Ysern, PhD

Division of Metabolism and Endocrine Drug Products HFD-510

Table of Contents

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-410

2. REVIEW # 1

3. REVIEW DATE: 24-MAY-2002

4. REVIEWER: Xavier Ysern

5. PREVIOUS DOCUMENTS:

Document(s)	Document Date
	07-MAR-2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	29-NOV-2001
Amendment	03-DEC-2001
	15-FEB-2002
	17-APR-2002
	24-APR-2002
	20-JUN-2002

1. NAME & ADDRESS OF APPLICANT:

Name:	GlaxoSmithKline (formerly SmithKline Beecham Corporation)
Address:	200 N. 16th Street
	Philadelphia, PA 19102
Representative:	Sharon W. Shapowal, R.Ph., Director US Regulatory Affairs
Telephone:	215 751 3434

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Avandamet
b) Non-Proprietary Name (USAN):	rosiglitazone maleate and metformin hydrochloride
c) Code Name:	SB-712753
d) Chem. Type/Submission Priority:	
▪ Chem. Type:	Type 4
▪ Submission Priority:	S

9. LEGAL BASIS FOR SUBMISSION: Not Applicable

10. PHARMACOLOGICAL CATEGORY: Proposed for the treatment of Type 2 diabetes mellitus as an adjunct to diet and exercise

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 1-mg/500-mg, 2-mg/500-mg, and 4-mg/500-mg

13. ROUTE OF ADMINISTRATION: Oral

Chemistry Review Data Sheet

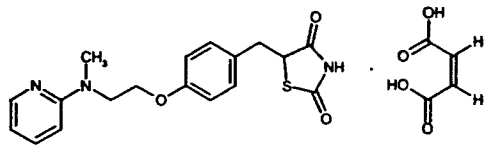
14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note29]: Not a SPOTS product

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

Rosiglitazone maleate

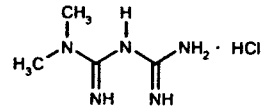
$C_{18}H_{19}N_3O_3S \cdot C_4H_4O_4$
MW = 357.4 + 116.1 = 473.5



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

Metformin Hydrochloride

$C_4H_{11}N_5 \cdot HCl$
MW = 129.17 + 36.46 = 165.63
CAS 657-25-9 (base) 1115-70-4 (hydrochloride)
N,N-Dimethylimidodicarbonimidic diamine monohydrochloride or *N,N*-Dimethylbiguanide HCl



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
				1	Adequate	12-MAR-2001	
				1	Adequate	09-APR-2002 09-APR-2002 09-APR-2002	
				4	Adequate		
				3	Adequate	01-APR-1999	
				3	Adequate	08-AUG-2001	
				4	Adequate		
				4	Adequate		
				3	Adequate	07-SEP-2001	DMF Strike Force Reviews
				3	Adequate	12-SEP-2000 18-SEP-2000 22-SEP-2000	
				4	Adequate		· GRAS material · Not in contact with the DP

[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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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)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-071	Rosiglitazone maleate

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	*Pending*		Office of Compliance
Biopharm	Dissolution review. *Pending*		Stephen Johnson, PhD HFD-870
ODC/DMETS LNC	*Does not recommend the use of proprietary name Avandamet*	11-APR-2002	Hye-Joo Kim, RPh HFD-420
Methods Validation	Drug product Assay (rosiglitazone content and Metformin HCl content) and Degradation (Rosiglitazone related and metformin related) methods will be sent for re-validation by Agency laboratories		
EA	The use of Avandamet tablets would not pose a threat to the environment	24-MAY-2002	Xavier Ysern, PhD HFD-820
Microbiology	N/A		

APPEARS THIS WAY ON ORIGINAL

Executive Summary Section

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is **can be approved** pending acceptable cGMP inspection of the SB Pharmco Puerto Rico facility.

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

None.

II. Summary of Chemistry Assessments

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

The **drug product, Avandamet Tablets** is a combination product of two active components, rosiglitazone and metformin. These two active components are antihyperglycemic agents that differ in both chemical class and mode of action. Rosiglitazone, a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPARγ), is a member of the thiazolidinedione class, and Metformin belongs to the biguanide class. Their mechanism of action is well understood, thiazolidinediones are insulin sensitizing agents that act primary by enhancing peripheral glucose utilization, whereas biguanides act primarily by decreasing endogenous hepatic output of glucose by inhibition of gluconeogenesis. Due to their complementary mechanisms of action, concurrent administration of rosiglitazone (Avandia (rosiglitazone) tablets) and metformin (Glucophage or generic metformin hydrochloride tablets) is frequently prescribed. The combination drug product will facilitate patient compliance.

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The tablet **formulation** was developed to provide fast release of the active ingredients. Three different strengths, **1-mg/500-mg, 2-mg/500-mg and 4-mg/500-mg** (rosiglitazone/metformin hydrochloride weight content), are proposed. Drug product manufacture is simplified by [redacted] A rosiglitazone [redacted], can be mixed with different proportions of an already prepared metformin [redacted] s to give [redacted] tablets of a desired strength. Although all core tablets have similar weight, size and shape. The three different strengths are easily distinguished by their color coating. The specification criteria of the combination product are consistent with those for Avandia® (rosiglitazone) tablets and for approved metformin tablets.

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stability studies show that the dosage form is compatibile with the packaging materials and reconfirm the expected stability of rosiglitazone maleate and metformin hydrochloride in solid oral tablet formulations.

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

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Avandamet tablets should be stored at controlled room temperature. Based on the available stability data and statistical analysis, at the recommended storage condition, the granted expiration dating is 18 months.

C. Basis for Approvability or Not-Approval Recommendation

There are no significant CMC deficiencies. Based on the evaluation of the information provided in the submission this application is **can be approved** from the Chemistry, Manufacturing and Control (CMC) standpoint, **pending an acceptable recommendation of the Office of Compliance.**

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-510/	Review Chemist	Xavier Ysern	
	Chemistry Team Leader	Stephen Moore	
	Project Manager	Jena Weber	/ 24-MAY-2002

C. CC Block

HFD-820/	NDCDII Director	Eric Duffy
	NDCDII Deputy Director	Duu Gong Wu

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

36 pages
+ 2 pages
38 pages

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
8/1/02 05:25:22 PM
CHEMIST

Stephen Moore
8/1/02 06:21:30 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

Table 18 Summary of Metformin HCl Pharmacokinetic Parameters in Bioequivalence Study 270

Formulation	Formula Code	Batch #	Dose (mg)	N	AUC (0-inf) [ng.h/mL]	C_{max} [ng/mL]	t_{max} [h]	$t_{1/2}$ [h]
500-mg metformin tablet and 4-mg Avandia tablet	N/A	U99009 2110A59	500 4	25	7413 (1838)	1135 (253)	2.50 (1.03 -3.98)	3.36 (0.54)
1-mg/500-mg tablet (commercial formulation)		N01025	1/500	24	6945 (2045)	1080 (327)	2.97 (1.00-5.98)	3.35 (0.59)
4-mg/500-mg tablet (commercial formulation)		N01032	4/500	25	7116 (2096)	1106 (329)	2.97 (1.02-4.02)	3.46 (0.96)

Pharmacokinetic parameters are expressed as mean (± SD), except t_{max}, which is median (range)

It has to be pointed out that the batches of 1-mg/500-mg and 4-mg/500-mg used in study 270 were manufactured at the commercial manufacturing site, — at approximately — of production scale, and are identical in formulation to the proposed commercial product including colors and tablet shape. Finally, **the adequacy of the bioequivalence study** including the acceptance of a waiver for the bioequivalence study for the lower and intermediate strength, Avandamet™ tablet 1-mg/500-mg and 2-mg/500-mg, **will be judged by the Biopharm Division.**

D. Environmental Assessment

Both rosiglitazone maleate and metformin hydrochloride, the two active components of Avandamet™ combination tablets, are not new molecular entities.

Rosiglitazone maleate is **categorically excluded from the Environmental Assessment (EA) requirement** as the Expected Introduction Concentration (EIC, the expected introduction concentration of the active moiety which may enter the environment due to disposal) into the environment is — [2] (data provided in amendment dated 17-APR-2002).

This criteria is accepted by the Agency to justify that the amount of this compound and/or its waste will be reasonable nontoxic. Finally, it is agreed with the applicant's conclusion that the use of metformin HCl drug substance resulting from approval of this action will not have negative effects on the environment.

Confidential information

Species	EC50 (mg/l)	NOEC (a) (mg/l)	MIC (b) (mg/l)	EC50 PEC	NOEC PEC	MIC PEC
Anebaena (algae), 96 hr acute						
Daphnia magna, 48 hr acute						
Bluegill sunfish, 96 hr acute						
Azobacter (N fixing bacterium)						
Microbial Inhibition (5 species)						
Activated Sludge, Respiration Inhibition (3 hr)						
Activated Sludge, COD Removal (24 hr)						
Activated Sludge, Nitrification Inhibition						

(a) no observed effect concentration
(b) minimum inhibitory concentration

Comment: As the two active components of Avandamet™ combination tables, rosiglitazone and metformin, are not new molecular entities, the EA section was not send for consult, it is reviewed by HFD-510 and part of this review.

Evaluation: The provided Environmental Assessment information is satisfactory. Based on current regulations, it is deemed that none of the two active ingredients, rosiglitazone or metformin, originated by the use of Avandamet™ tablets would pose a threat to the environment.

E. Methods Validation

The section describing the validation of the analytical method is adequately provided. A copy of this section, "Methods Validation Package", which provides a description of the tests and their validation, will be sent to the Agency laboratories for revalidation. The analytical tests were discussed in the specification section of this review. As some of the methods are well established, not all analytical methods will be requested for revalidation. *Only the methods to assay the active components rosiglitazone and metformin in the drug product, and the methods to determine their corresponding degradation products, will be requested for revalidation*

F. Labeling

The proposed labeling for Avandamet™ Tablets is provided in the "Labeling-Proposed" section of the submission. The **chemistry pertinent sections** of the packaging insert, "Description" and "How Supplied", are **adequately described**. Commercial presentations are summarized in table 19.

Copies of the container labels (1mg/500mg Bottles of 60, 1mg/500mg Bottles of 100, 2mg/500mg Bottles of 60, 2mg/500mg Bottles of 100, 2mg/500mg Bottles of 500, 4mg/500mg Bottles of 60, 4mg/500mg Bottles of 100, and 4mg/500mg Bottles of 500) are provided in the original submission. Updated carton and foil labeling for the courtesy samples 14 tablet count) are provided in the 20-JUN-2002 amendment. Representative labels are shown in figures 11 and 12. The **storage condition** "Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F)" is **adequately stated on the packaging insert and labels.** In addition to the temperature recommendation, the package insert and container have the dispensing recommendation "Dispense in a tight, light-resistant container".

G. Establishment Inspection *Satisfactory*

As of date 24-MAY-2002 (CMC review # 1), GSB's Cork (Ireland) and SB Pharmco Puerto Rico Inc. facilities were still pending. The **SB Pharmo Puerto Rico Inc.** was listed in the OAI Alert section, and a **withhold recommendation** was **issued** on 09-APR-2002. **These two facilities are now acceptable.** Based on District Recommendations, GSB's Cork (Ireland) and SB Pharmco Puerto Rico Inc. facilities were given an acceptable cGMP status by the Office of Complaince (October 1 and 10, 2002, respectively). EER dated 10-OCT-2002 is attached.

Manufacturing Facilities

Manufacturing Responsability	*Facility Name and Address*	*CFN*	*Status*	*Date*
Rosiglitazone maleate DS	GlaxoSmithKline (Cork) Limited Curranbinny Carrigaline, Co. Cork IRELAND	9610176	Acceptable	01-OCT-2002
[redacted]	[redacted]		Acceptable	25-JUN-2002
AVANDAMET™ tablets DP	SB Pharmco Puerto Rico Inc. Road 172, Km. 9.1 Post Office Box 11975 Cidra, Puerto Rico 00739-1975	2650232	Acceptable	10-OCT-2002

Attached :

EER Summary Report (2 pages)

APPEARS THIS WAY ON ORIGINAL

10-OCT-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21410/000
Stamp: 29-NOV-2001 Regulatory Due: 10-OCT-2002
Applicant: GLAXOSMITHKLINE
5 MOORE DR
RESEARCH TRIANGLE PARK, NC 27

Priority: 4S Org Code: 510
Action Goal: District Goal: 11-AUG-2002
Brand Name: ROSIGLITAZONE MALEATE/METFORMIN HCL TAB
Established Name:
Generic Name: ROSIGLITAZONE MALEATE/METFORMIN HCL TAB
Dosage Form: TAB (TABLET)
Strength: 1/500, 2/500 & 4/500 MG

FDA Contacts:
S. MOORE (HFD-510) 301-827-6430 , Project Manager
X. YSERN (HFD-510) 301-827-6420 , Review Chemist
J. WEBER (HFD-510) 301-827-6422 , Team Leader

Overall Recommendation:

Establishment: [redacted]
DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 25-JUN-2002
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: [redacted]

Establishment: 9610411
GLAXO OPERATIONS UK LTD
WARE, HERTFORDSHIRE, UK
DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: INSPECTION PERFORMED
Milestone Date: 19-SEP-2002

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Establishment: 9610176
GLAXOSMITHKLINE
CURRAGHBINNY
COUNTY CORK, , EI
DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-OCT-2002

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

10-OCT-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

DRUG SUBSTANCE STABILITY TESTER

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **2650232**
SB PHARMCO PUERTO RICO INC
RD 172 KM 9.1 BO CERTENEJAS
CIDRA, PR 007391975

DMF No:
AADA No:

Profile: **TCM** OAI Status: **POTENTIAL OAI**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **10-OCT-2002**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

APPEARS THIS WAY
ON ORIGINAL