CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-410

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: 21-410

Name of Drug: Avandamet (rosiglitazone and metformin HCl) Tablets
1 mg/500 mg; 2 mg/500 mg; 4 mg/500mg

Sponsor: GlaxoSmithKline, Inc.

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Combination

Submission Date: November 29, 2001 **Receipt Date:** November 29, 2001
Unacceptable for Filing: December 5, 2001 **Payment Accepted:** December 10, 2001

Filing Date: December 10, 2001 **User-fee Goal Date:** October 10, 2002

Proposed Indication: As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

Other Background Information: This application is a combination product consisting of two approved products: NDA 20-357 metformin HCL (approved March 5, 1995), and NDA 21-071 rosiglitazone maleate (approved May 25, 1999).

Review

PART I: OVERALL FORMATTING[a,d,e]

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	✔		Volume 1
2. Form FDA 356h (original signature)	✔		Volume 1
a. Establishment information b. (facilities ready for inspection?)	✔		Drug substance manufacturing facility ready Feburauy 2002. Volumes 1- 4 Inspection set for July 2002

b. Reference to DMF(s) & Other Applications	✔		Volume 1
3. User Fee FDA Form 3397 4. Patent information & certification	✔		Volume 1 Volume 1
5. Debarment certification (Note: Must have a definitive statement)	✔		Volume 1
6. Field Copy Certification	✔		Volume 1
7. Financial Disclosure	✔		Volume 1
8. Comprehensive Index	✔		Volume 1
9. Pagination	✔		
10. Summary Volume	✔		Volume 1, Item 3
11. Review Volumes	✔		
12. Labeling (PI, container, & carton labels)	✔		Volume 1
a. unannotated PI	✔		Volume 1
b. annotated PI	✔		Volume 1
c. immediate container	✔		Volume 1
d. carton	✔		Volume 1
e. patient package insert (PPI)	✔		Volume 1
f. foreign labeling (English translation)		✔	N/A
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	✔		Crt\datasets\270\define\pdf Crt\datasets\271\define\pdf
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)		✔	N/A

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	✔		Volume 1
2. Foreign Marketing History	✔		Volume 1
3. Summary of Each Technical Section	✔		Volume 1
a. Chemistry, Manufacturing, & Controls (CMC)	✔		Requesting 25 months expiry for all packages. Volumes 1 – 4
b. Nonclinical Pharmacology/Toxicology		✔	Reference NDA 21-071; no cross-reference to metformin. Volume 1
c. Human Pharmacokinetic & Bioavailability	✔		Food effects study and BQ provided; Study #270 and Study 271. Volumes 1 – 4
d. Microbiology		✔	N/A
e. Clinical Data & Results of Statistical Analysis		✔	No clinical data submitted; available by cross-reference only to NDA 21-071
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	✔		Volume 1
5. Summary of Safety	✔		From NDA 21-071; Volume 1.8
6. Summary of Efficacy	✔		From NDA 21-071; Volume 1.8

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators	✔		Volume 1, Financial information
2. Controlled Clinical Studies		✔	N/A
a. Table of all studies		✔	N/A
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)		✔	N/A
c. Optional overall summary & evaluation of data from controlled clinical studies		✔	N/A
3. Integrated Summary of Efficacy (ISE)	✔		From NDA 21-071; Volume 1.8
4. Integrated Summary of Safety (ISS)	✔		From NDA 21-071; Volume 1.8
5. Drug Abuse & Overdosage Information		✔	N/A
6. Integrated Summary of Benefits & Risks of the Drug		✔	N/A
7. Gender/Race/Age Safety & Efficacy Analysis of Studies		✔	N/A

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS[d,e]

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population	✔		Deferral requested in cover letter Volume 1
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)		✔	
a. Proposed unannotated labeling in MS WORD	✔		Volume 1
b. Stability data in SAS data set format (only if paper submission)		✔	N/A
c. Efficacy data in SAS data set format (only if paper submission)		✔	N/A
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		✔	N/A
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		✔	N/A
3. Exclusivity Statement (optional)		✔	N/A

Y=Yes (Present), N=No (Absent)

[a]"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[b]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[c]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

[d]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

[e]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

Conclusions: AP NDA

Name
Regulatory Project Manager

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

/s/

Jena Weber
10/11/02 12:29:00 PM
CSO

Jena Weber
10/11/02 12:31:37 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

NDA REGULATORY FILING REVIEW

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type):

NDA 21-410
AVANDAMET
Rosiglitazone/metformin HCl tablets
1 mg/500 mg; 2 mg/500 mg; 4 mg/500mg

Applicant: GlaxoSmithKline

Date of Application: 11/29/01
Date of Receipt: 11/29/01
UN date: 12/5/01
Acceptable for Filing: 12/10/01
Date of Filing Meeting: 1/09/02
Filing Date: 2/08/02

Indication(s) requested: As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

Type of Application: Full NDA __✔_ Supplement ___
(b)(1) _✔_ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classifications: S_✔_ P_
Resubmission after a withdrawal or refuse to file _✔_(UN)_
Chemical Classification: (1,2,3 etc.)__4____
Other (orphan, OTC, etc.)____N/A_____

User Fee Status: Paid _✔_ Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES
User Fee ID#___4181__
Clinical data? NO; Reference clinical data contained in original application (NDA 21-071)

Date clock started after UN: 12/10/01

User Fee Goal date: 10/10/02

Action Goal Date (optional)

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

- Does the submission contain an accurate comprehensive index? YES

- Form 356h included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

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

- If electronic NDA, does it follow the Guidance? YES

- Patent information included with authorized signature? YES

- Exclusivity requested? NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. 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 the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- Financial Disclosure included with authorized signature? YES
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

- Pediatric Rule appears to be addressed for all indications? NO Deferral requested.

- Pediatric assessment of all ages? NO
  (If multiple indications, answer for each indication.)
  If NO, for what ages was a waiver requested? _____
  For what ages was a deferral requested? _____

- 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 DSS? 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/DSS? YES

List referenced IND numbers: ———

End-of-Phase 2 Meeting? NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? NO
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? YES

Trade name and labeling (PI) sent to ODS? YES

Advisory Committee Meeting needed? NO

Clinical

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

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES

  If no, did sponsor submit a complete environmental assessment? N/A

- EA consulted to Nancy Sager (HFD-357)? NO

- Establishment Evaluation Request (EER) package submitted? YES

- Parenteral Applications Consulted to Sterile Products (HFD-805)? N/A

505(b)(2) NA

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").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)?
Yes ____ No _____
(Normally, FDA will refuse-to-file such applications.)

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)?
Yes _____ No _____
If yes, the application must be refused for filing under 314.54(b)(1)

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?
Yes _____ No _____
If yes, the application must be refused for filing under 314.54(b)(2)

For a 505(b)(2) application, which of the following 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): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for 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.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

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?

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

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

If the application is a 505(b)(2), has the Director, Div. of Regulatory Policy II, HFD-007 been notified? YES _____ NO _____

ATTACHMENT

FILING MEETING MINUTES

DATE: Monday January 21, 2002

BACKGROUND: Combination product (Avandamet) to treat patients with type 2 DM. Avandia (rosiglitazone maleate) + metformin HCl. FDA action will be based upon data from two trials; a bioequivalence study and a food effects study.

ATTENDEES: Xavier Ysern, Steven Johnson, Kati Johnson, Joanna Zawadzki, Jena Weber

ASSIGNED REVIEWERS:

Discipline	Reviewer
Medical:	Joanna Zawadzki - for LBL only
Secondary Medical:	N/A
Statistical:	N/A
Pharmacology:	N/A
Statistical Pharmacology:	N/A
Chemist:	Xavier Ysern, Stephen Moore
Environmental Assessment (if needed):	N/A
Biopharmaceutcal:	Steven Johnson, Hae-Young Ahn
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	C.T. Viswanathan, Martin Yau
Project Manager:	Jena Weber
Other Consults:	Sammie Beam (OPDRA) Karen Lechner (ODS)

Is the application affected by the application integrity policy (AIP) NO

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

CLINICAL – N/A

- Clinical site inspection needed: N/A

MICROBIOLOGY CLINICAL – N/A

STATISTICAL – N/A

BIOPHARMACEUTICS – File _✔

- Biopharm. inspection Needed: YES

PHARMACOLOGY – N/A

CHEMISTRY –

- Establishment ready for inspection? YES File_✔

REGULATORY CONCLUSIONS/DEFICIENCIES:

✔__The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

___ The application is unsuitable for filing. Explain why:

PM Notes:

Medical reviewer to evaluate package insert labeling and PPI, after other reviews have been completed.
DSI to review both studies submitted by the company. GSK is asking for biowaiver of 2 strengths; we will need more information on the dissolution profiles to make this determination.
Tradename to be sent for review and comment from OPS.

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

/s/

Jena Weber
10/11/02 12:43:36 PM
CSO

Jena Weber
10/11/02 12:46:21 PM
CSO

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

SmithKline Beecham Corporation
200 North 16th Street
Philadelphia, PA 19102

2. TELEPHONE NUMBER *(Include Area Code)*

(215) 751-3434

3. PRODUCT NAME

AVANDAMET (rosiglitazone maleate/metformin hydrochloride)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-410

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:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4181

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 COMMERCIALLY
(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
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
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	TITLE	DATE
Sharon W. Shapowal	Sharon W. Shapowal, R.Ph Director, U.S. Regulatory Affairs	November 12, 2001

FORM FDA 3397 (3/01)

Created by: PSC Media Arts (301) 443-2454 EF

11/13/2001 21:22 FAX SKB 003

04102 Manual Payment w/Voucher Match Prev Paymt:

Print Payment. . _
Action Code. . . I
Supplier Number. _____ FOOD AND DRUG ADMINISTRATION
Payment Number . 1060072 G/L Bank 100.1720.014
Payment Amount . 154,823.00 Remark _____
Payment-G/L Date 11/15/01

Batch Number 1545977

Remaining. . . .

. . . . . Payment Schedule . . . . . .

Voucher Number	Pay Itm	Invoice Number	Net Due Date	Amount Applied	Discount Taken
_____	001	NDA 21-410	11/13/01	154,823.00	

F4=Details F16=Ledger Inq F11=Supplier F9=Name Srch F17=Void F24=More

APPEARS THIS WAY
ON ORIGINAL

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-410		Supplement Number N/A	
Drug: Avandamet (rosiglitazone & metformin HCl) tablets		Applicant: GlaxoSmithKline	
RPM: J.Weber		HFD-510	Phone # 76422
Application Type: (✔) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug: Avandamet, NDA 21-410	

❖ Application Classifications:	
• Review priority	(✔) Standard ( ) Priority
• Chem class (NDAs only)	4
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	October 10, 2002
❖ Special programs (indicate all that apply)	(✔) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(✔) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (✔) No
• This application is on the AIP	( ) Yes (✔) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(✔) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(✔) Verified 314.53
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	✔
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	✔

General Information	
❖ Actions	
• Proposed action	(✔) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(✔) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (✔) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(✔) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	✔10/9/02 final clean draft
• Original applicant-proposed labeling	✔
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	ODS – 5/24/02, /8/28/02 PPI/carton/container LBL OPDRA 5/10/02 Tradename
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	✔
• Reviews	✔
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	NO
• Documentation of discussions and/or agreements relating to post-marketing commitments	NO
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✔
❖ Memoranda and Telecons	✔
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A – not an NME
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Divisi on Director, Medical Team Leader) *(indicate date for each review)*	Division Director: 10/10/02
❖ Clinical review(s) *(indicate date for each review)*	N/A – by cross reference to NDA 21-071
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	9/26/02 (MO)
❖ Statistical review(s) *(indicate date for each review)*	N/A
❖ Biopharmaceutical review(s) *(indicate date for each review)*	8/30/02 – AP
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A – by cross reference to NDA 21-071
• Bioequivalence studies	7/2/02, 7/26/02
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	Rec. 8/1/02 – AP; revised 10/10/02 - AP
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	8/1/02
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	8/1/02
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: (✔) Acceptable ( ) Withhold recommendation
❖ Methods validation	(✔) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A – by cross reference to NDA 21-071
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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

/s/

Jena Weber
10/11/02 01:04:26 PM

APPEARS THIS WAY
ON ORIGINAL

Division of Metabolic and Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW

Application Numbers: 21-410 Avandamet (rosiglitazone maleate and metformin HCl) Tablets 1 mg/500 mg; 2 mg/500 mg; 4 mg/500 mg.

Sponsor: GlaxoSmithKline, Inc.

Material Reviewed: Draft package insert (PI); draft patient package insert (PPI); final carton and container labels.

Submission Date: November 29, 2001 **Receipt Date:** November 29, 2001

Background and Summary Description: Avandamet is a fixed-dose combination product of two different active ingredients consisting of rosiglitazone maleate and metformin hydrochloride tablets. It is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. Rosiglitazone maleate (Avandia®) was approved under NDA 21-071 on May 25, 1999. Metformin HCl (Gluophage®) was approved under NDA 20-357, on March 5, 1995.

Review: The final draft **PI** (identifier code: AT:LV) was submitted by GSK on October 2, 2002, and was found acceptable by DMEDP on October 4, 2002. The final "clean" draft was provided by the company on October 9, 2002. The only modification was the removal of

. GSK and DMEDP agreed on the content of the PPI document, and it was decided that they could distribute this as it appeared in the original NDA submission. The final "clean" draft was submitted on October 9, 2002, and found acceptable by DMEDP. It should be noted that the company did not implement the new format for PPI's as suggested in the consult reviews from the Office of Drug Safety. Regardless, since there is no official policy or guidance available to sponsor's to aid them in preparing this document, DMEDP did not find it necessary to request that the company alter the appearance of this text. The FPL identifier code for the PI is AT:L1.
The final carton labels (that included revisions requested by Office of Drug Safety are acceptable).

Container Labels:

4 mg/500 mg; 500 tablet count, NDC 0007-3168-25, revised 8/02
4 mg/500 mg; 100 tablet count, NDC 0007-3168-20, revised 8/02
4 mg/500 mg; 60 tablet count, NDC 0007-3168-18, revised 8/02
2 mg/500 mg; 500 tablet count, NDC 0007-3167-25, revised 8/02
2 mg/500 mg; 100 tablet count, NDC 0007-3167-20, revised 8/02

2 mg/500 mg; 60 tablet count, NDC 0007-3167-18, revised 8/02
1 mg/500 mg; 100 tablet count, NDC 0007-3166-20, revised 8/02
1 mg/500 mg; 60 tablet count, NDC 0007-3166-18, revised 8/02

Unit Dose:

4 mg/500 mg; 100 tablet count, NDC 0007-3168-21, revised 8/02
2 mg/500 mg; 100 tablet count, NDC 0007-3167-21, revised 8/02
1 mg/500 mg; 100 tablet count, NDC 0007-3166-21, revised 8/02

Unit Dose Sample Foils:

4 mg/500 mg; 7 tablet count, NOT FOR SALE, 738948-B, revised 8/02
2 mg/500 mg; 7 tablet count, NOT FOR SALE, 738947-B, revised 8/02
1 mg/500 mg; 7 tablet count, NOT FOR SALE, 738946-B, revised 8/02

Container:

4 mg/500 mg; 14 tablet count, SAMPLE – NOT FOR SALE, NDC 0007-3168-61, revised 8/02
2 mg/500 mg; 14 tablet count, SAMPLE – NOT FOR SALE, NDC 0007-3167-61, revised 8/02
1 mg/500 mg; 14 tablet count, SAMPLE – NOT FOR SALE, NDC 0007-3166-61, revised 8/02

Unit Dose Foil Packages:

4 mg/500 mg; per tablet, 731993-A, revised 8/02
2 mg/500 mg; per tablet, 731992-A, revised 8/02
1 mg/500 mg; per tablet, 731001-A, revised 8/02

All the above labels are acceptable; however, the sample unit dose foil package will be revised at the next printing to include a space between the number and the "mg." For example, revise to read " 1 mg/500 mg," rather than '

Conclusions: An approval (AP) letter should be issued; request FPL.

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ON ORIGINAL

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/s/

Jena Weber
10/11/02 02:35:51 PM
CSO

Jena Weber
10/11/02 02:39:56 PM
CSO

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ON ORIGINAL

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Office of Drug Safety (DMETS) Attention: Alina Mahmud, HFD-400			FROM: Division of Metabolic and Endocrine Drug Products Attention: Jena Weber, HFD-510	
8/23/02	IND NO. N/A	NDA NO. 21-410	TYPE OF DOCUMENT LBL	DATE OF DOCUMENT: 8/14/02
NAME OF DRUG Avandamet	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG Oral anti-diabetic agent	DESIRED COMPLETION DATE: 9/15/02

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ✓ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ SOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: See attached response from company. This was in reply to our fax to them dated 7/31/02 that included comments/requests from DMETS.

SIGNATURE OF REQUESTER: Jena Weber (x76422)	METHOD OF DELIVERY (Check one) DFS
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Alina Mahmud
8/27/02 09:26:18 AM

APPEARS THIS WAY
ON ORIGINAL

Office of Drug Safety

Memo

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

From: Hye-Joo Kim, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Through: Alina Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
HFD-420

CC: Jena Weber
Project Manager
HFD-510

Date: August 22, 2002

Re: ODS Consult 01-0175-1; Avandamet (Rosiglitazone Maleate and Metformin HCl Tablets); NDA 21-410

This memorandum is in response to an August 21, 2002 request from your Division to provide any comments to the label/labeling revisions provided by the sponsor, GlaxoSmithKline. DMETS originally reviewed the labels/labeling of Avandamet and recommended revisions that may minimize potential errors with the use of this product on April 11, 2002 (ODS consult 01-0175). The sponsor agreed to make all the revisions we requested in the original review except the following (see page 2):

1. Sponsor's Response:

GSK agrees to remove the red triangle from the Avandamet logo presently shown on the Commercial Bottle Labels of 60, 100, and 500 tablets **"and the SUP Carton Label."** We propose to not delete the red triangle from the Avandamet logo on the Sample Foils and Sample Cartons, as these are promotional samples that are NOT for SALE. We have previously followed this approach with Avandia. GSK regards Avandamet as an important member of the Avandia family and in order to maintain consistency across products, we request your agreement to leave the red triangle on the Avandamet logo for the Sample Foils and Sample Carton.

DMETS Response:

We agree with the sponsor GSK that the red triangle from the Avandamet logo does not have to be deleted from the sample foils and sample cartons, since these are promotional items and are "not for sale." Additionally, these promotional samples are not stocked in pharmacies to be dispensed to patients.

2. Sponsor's Response:

This (unit-dose) packaging is not child-resistant. It is not child resistant because the SUP presentation will only be prepared by the healthcare provider and distributed to the patient, a single dose at a time. It is for this reason that GSK does not consider this statement necessary on this presentation. However, GSK will include such a statement should DMETS regard it a necessary on this presentation.

DMETS Response:

DMETS originally requested the sponsor to include a statement as to whether or not the unit-dose packaging is child resistant. However, we agree with the sponsor that the unit-dose packaging intended only for the institutional practices, such as a nursing home or hospital, is exempt from the Poison Prevention Packaging Act. Therefore, the statement that the unit-dose package is not child-resistant is not deemed necessary on the carton labeling of the unit dose.

Additionally, DMETS has reviewed the *revised* unit dose labels, container labels, carton labeling, and have the following comment:

> UNIT DOSE LABELS and CARTON LABELING (100's) (1 mg/500 mg, 2 mg/500 mg, and 4 mg/500 mg)
>
> Insert a space between the number and "mg". For example, revise to read " 1 mg/500 mg" rather than 1mg

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussions as well. If you have any questions or need clarification, please contact the project manager, Sammie Beam at 301-827-3242.

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/s/

Hye-Joo Kim
8/28/02 10:42:24 AM
PHARMACIST

Alina Mahmud
8/28/02 10:54:01 AM
PHARMACIST

Carol Holquist
8/28/02 11:17:31 AM
PHARMACIST

Jerry Phillips
8/28/02 11:23:28 AM
DIRECTOR

MEMORANDUM

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

DATE: June 10, 2002

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

TO: NDA 21-410
Avandamet (rosiglitazone maleate and metformin)
Glaxo-SmithKline
Treatment of type 2 diabetes

SUBJECT: Division decision on proposed name

The Division of Medication Errors and Technical Support, ODS, has recommended against the name Avandamet, primarily because of potential sound-alike, look-alike confusion with Aldomet (alphamethyldopa), an old anti-hypertensive drug. Specifically, there is concern that the 1/, 2/, or 4/500 mg strengths of Avandamet might be inadvertently substituted with the 500 mg strength of Aldomet.

The sponsor has responded to this concern with prescribing information for Aldomet. This is a drug that enjoys only limited use at this time, with [redacted] prescriptions annually for the 500 mg strength. As such, it is clear that very few pharmacies around the country will even have Aldomet on their shelves. It is therefore unlikely that pharmacists will confuse the two. I see little risk of medication errors.

Recommendation
The name Avandamet is acceptable.

NDA #
Drug:
Proposal:
06/10/02

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/s/

David Orloff
6/10/02 01:06:52 PM
MEDICAL OFFICER

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ON ORIGINAL

MEMO TO THE FILE

May 20, 2002; amended May 29, 2002

NDA #: 21-410

RE: **Product Name**
Avandamet (rosiglitazone maleate and metformin HCl Tablets),
GlaxoSmithKline

Summary:

The Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name *Avandamet* and recommended against the usage of this proprietary name.

The primary concerns raised were existing proprietary drug names that sounded and looked like the proposed name *Avandamet*, including *Aldomet* (methyldopa, Merck – for treatment of hypertension), *Avandia* (rosiglitazone, GSK – one of the components of *Avandame*), *Avapro* (irbesartan, for the treatment of hypertension), *Anzemet* (dolasetron, given by injection for the treatment of nausea and vomiting), and [redacted]. Please see the DMETS consult review (dated 5/13/02) for a detailed analysis of these comparator drugs and specific comments to the sponsor.

This DMETS recommendation was discussed in the Division of Metabolic and Endocrine Drug Products (DMEDP) and initially there was concurrence with the recommendation. On May 17, 2002, the sponsor forwarded a facsimile (received May 23, 2002 by this reviewer) with prescribing information regarding *Aldomet*. The sponsor reported that there were [redacted] prescriptions "in the past year" (presumably 2001), of which [redacted] were for *Aldomet* 500 mg.

This number is quite small, partially because the generic drug methyldopa is probably more commonly prescribed currently. However, there is still a possible confusion between the names *Avandamet* and *Aldomet* that may be a clinical concern. This confusion evolves from the similar sounds of these two names, the proximity of these drugs in the dispensing pharmacist's drawers, the similarity of the colors [*Avandamet* 1/500 mg yellow oval, 2/500 mg pink oval, 4/500 mg orange oval tablets; *Aldomet* 125 mg small yellow round, 250 medium yellow round, 500 mg large yellow round tablets]. The distinctly different indications of the drugs accentuate the clinical concern. The name *Avandamet* could also be confused with the generic name for another anti-hypertensive drug aldactone, but there is less similarity between these two names.

This reviewer recognizes that though the likelihood of confusion is small, the name *Avandamet* may be confused with the names of other proprietary drugs and needs to be changed. This decision is an opinion, and the recommendation regarding the final proprietory name should be made by the DMEDP division director.

Joanna K. Zawadzki, M.D.

Cc David G. Orloff, M.D.
Division Director, DMEDP

Jena Weber, Project Manager, DMEDP

Carol Holquist, RPh
Deputy Director, DMETS

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/s/

Joanna Zawadzki
5/30/02 04:04:15 PM
MEDICAL OFFICER

David Orloff
6/4/02 07:07:28 PM
MEDICAL OFFICER
Do not concur with reviewer. The principal concern with regard to medication error relates to Aldomet 500 mg. [redacted]. Rx's were filled in the US last year. I see minimal likelihood of confusion of Avandamet with Aldomet resulting in errors. DGO

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)

DATE RECEIVED: 7/24/01	DUE DATE: 5/10/02	ODS CONSULT #: 01-0175

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

THROUGH: Jena Weber
Project Manager
HFD-510

PRODUCT NAME: **Avandamet** (Rosiglitzone Maleate and Metformin HCl Tablets) 1 mg/500 mg, 2 mg/500 mg, and 4 mg/500 mg NDA #: 21-410	NDA SPONSOR: GlaxoSmithKline

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

MMARY: In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Avandamet" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS does not recommend the use of the proprietary name, Avandamet. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 11, 2002

NDA #: 21-410

NAME OF DRUG: **Avandamet**
(Rosiglitzone Maleate and Metformin HCl Tablets)
1 mg/500 mg, 2 mg/500 mg, and 4 mg/500 mg

NDA HOLDER: GlaxoSmithKline

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult is written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510) for an assessment of the proposed proprietary name, Avandamet. The container labels, carton and package insert labeling were reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

Avandamet contains two oral antihyperglycemic drugs, metformin hydrochloride and rosiglitazone maleate. Avandamet is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. Avandamet should be individualized on the basis of effectiveness and tolerability while not exceeding the maximum recommended daily dose of 8 mg/2000 mg. Avandamet should be given in divided doses with meals, with gradual dose escalation. The usual starting dose is 2 mg/500 mg to 4 mg/500 mg twice daily. Avandamet will be supplied as 1 mg/500 mg, 2 mg/500 mg, and 4 mg/500 mg tablets.

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 databases[3] for existing drug names which sound-alike or look-alike to "Avandamet" 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[4] and the Saegis[5] Pharma-In-Use database were also conducted. 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, outpatient and inpatient, 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

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Avandamet. Potential concerns regarding drug marketing and promotion related to the proposed names 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. The Expert Panel identified several names that were thought to have the potential for confusion with Avandamet. These products are listed in table 1 (see page 4), along with the dosage forms available and usual dosage.

2. DDMAC did not have any concerns about the name with regard to promotional claims.

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

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

[3] The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, 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 and Thomson' SAEGIS™ Online Service, available at www.thomson-thomson.com.

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

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Avandamet	Rosiglitazone Maleate/Metformin HCL Tablet; 1 mg/500 mg, 2 mg/500 mg, and 4 mg/500 mg	Initial Therapy: 2 mg/500 mg to 4 mg/500 mg BID. Maximum Dose: 8 mg/2000 mg, in divided doses with meals.	
Aldomet	Methyldopa Tablet; 125 mg, 250 mg, and 500 mg	Initial Therapy: 250 mg BID to TID Maintenance Therapy: 500 mg to 2000 mg in two to four doses.	SA/LA
Avandia	Rosiglitazone Maleate Tablet; 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.	SA/LA
Avapro	Irbesartan Tablet; 75 mg, 150 mg, and 300 mg	75 mg to 300 mg QD.	LA
Anzemet	Dolasetron Mesylate; Injection: 12.5 mg/0.625 mL and 100 mg/5 mL Tablet: 50 mg and 100 mg	Prevention of Cancer Chemotherapy-Induced Nausea and Vomiting: 100 mg IV 30 minutes before chemotherapy. 100 mg PO within 1 hour before chemotherapy. Prevention or Treatment of Postoperative Nausea and/or Vomiting: 12.5 mg IV 15 minutes before cessation of anesthesia. 100 mg PO within two hours before surgery.	SA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Avandamet with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 113 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 Avandamet (see page 5). 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.

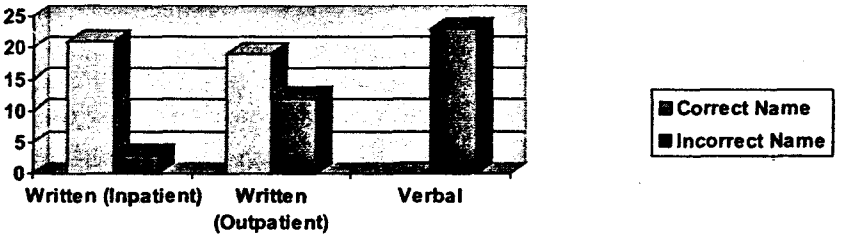
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Avandamet 2/500 mg s.s. + bid #60	Avandamet 2 mg/500 mg Take 1 tablet twice daily. #60
Inpatient RX: ~~[illegible]~~ Avandamet 2/500mg bid	

2. Results:

The results are summarized in Table 2

Table 2 (AVANDAMET)

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	34	24 (71%)	21 (88%)	3 (12%)
Written Outpatient	40	31 (78%)	19 (61%)	12 (39%)
Verbal	39	23 (59%)	0 (0%)	23 (100%)
Total	113	78 (69%)	40 (51%)	38 (49%)



Among the verbal prescription study participants for **Avandamet**, 23 of 23 (100 %) participants interpreted the name incorrectly. The majority of the incorrect name interpretations were phonetic variations of "Avandamet." The incorrect responses were *Advantamet (7), Advanamet (4), Advantomet (1), Avanamet (1), Ativmet (1), Advanimet (2), Advantemit (1), Advadamet (1), Advenamet (1), Avantamet (1), Advanemet (1), Advantimant (1),* and *Avandament (1).*

Among the written prescription study participants for **Avandamet**, 15 of 55 (27%) participants interpreted the name incorrectly. *One participant from the outpatient written study interpreted the name incorrectly as "Aldomet," an approved drug product.* The majority of the other responses were misspelled variations of "Avandamet." Other incorrect responses were *Avandomet (2),Avardamet (2), Aumdamit (1), Avandamit (1), Amolamet (1), Avandemet (1), Avanlamet (1), Avasdamet (1), Avardamet (1), Avandames (1), Alandamet (1),* and

Avandomet (1).

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Avandamet", the primary concerns raised were related to sound-alike and look-alike names that already exist in the U.S. marketplace. The products considered having the greatest potential for name confusion with Avandamet were Aldomet, Avandia, Avapro, Anzemet, and ——

We conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Avandamet could be confused with **Aldomet.** *One participant from the outpatient written study interpreted the name as Aldomet, an approved drug product.* Although there are limitations to the predictive value of these studies, primarily due to the small 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.

Aldomet contains the active ingredient, methyldopa, and is indicated in the management of hypertension. Aldomet is dosed 500 mg to 2000 mg daily in two to four doses. The proposed name Avandamet looks and sounds similar to Aldomet as they both begin with the letter "A" and end with similar letter combinations, "damet" and "domet" (see below). In fact, one participant from the outpatient written study interpreted the proposed name as Aldomet. We acknowledge that Avandamet contains two active ingredients and will be available as 1 mg/500 mg, 2 mg/500 mg, and 4 mg/500 mg combination strength tablets. Aldomet, on the other hand, contains one active ingredient and is available in 125 mg, 250 mg, and 500 mg single strength tablets. However, there is a similar strength (500 mg) between Avandamet and Aldomet. Furthermore, Avandamet and Aldomet share overlapping dosing intervals (BID and TID). Lastly, a prescription for "Avandamet 1 mg/500 mg TID" may be written as "Avandamet 1/500 mg TID", and this can be easily misinterpreted as "Aldomet 1 tablet of 500 mg TID". Moreover, a verbal prescription for "Avandamet 1/500 mg TID" may be heard as "Aldomet one five hundred milligram three times daily".

Avandamet 1/500 mg TID

Aldomet 500 mg TID

The inadvertent ingestion of Avandamet can result in serious toxicity. Metformin contained in Avandamet has the following black box warning: "Lactic acidosis is rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with Avandamet; when it occurs, it is fatal in approximately 50% of cases." Furthermore, Avandamet has been associated with anemia, hypoglycemia, and diarrhea. If a patient receives Aldomet instead of Avandamet, a patient can experience various adverse events associated with antihypertensive agents, including orthostatic hypotension, bradycardia, dizziness, fatigue, and headache. Lastly, a positive Coombs test, hemolytic anemia, and liver disorders have been associated with the Aldomet therapy.

Avandia contains one of the active ingredients of Avandamet, rosiglitazone maleate. Avandia, a thiazolidinedione oral antidiabetic agent, is indicated as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes mellitus. The recommended usual starting dose is 4 mg as a single daily dose or divided and administered in the morning and evening. Avandia is available as 2 mg, 4 mg, and 8 mg tablets. Avandia and Avandamet share the same prefix "Avand". Moreover, since Avandamet also contains rosiglitazone, Avandia and Avandamet share similar strengths, "2 mg" and "4 mg". Furthermore, they share an overlapping dosing interval (BID). The strength of metformin in Avandamet differentiates these two drugs, however, all Avandamet drug products contain 500 mg of metformin: 1 mg/500 mg, 2 mg/500 mg, and 4 mg/500 mg. Therefore, a prescription for Avandamet can be ordered without the metformin strength, "500 mg." For instance, a prescription for "Avandamet 2 mg/500 mg BID" may be written as "Avandamet 2 mg BID" and this can be misinterpreted as "Avandia 2 mg BID" or vice versa (see below).

Avandamet 2mg BID #60 Avandia 2mg BID #60

Lastly, Avandamet will be placed in close proximity to Avandia on pharmacy shelves, further increasing the risk of errors. If a patient inadvertently receives Avandamet instead of Avandia, she can experience inappropriate treatment for diabetes. Furthermore, if a patient is already on metformin, she may be at an increased risk for lactic acidosis due to the additional metformin contained in Avandamet. Metformin has the following black box warning: "Lactic acidosis is rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with Avandamet; when it occurs, it is fatal in approximately 50% of cases." If a patient receives Avandia instead of Avandamet, she can experience inappropriate treatment for the existing condition due to the lack of metformin treatment in Avandia.

[redacted] . Avandamet and [redacted] . can sound and look similar; both proprietary names contain four syllables and the prefix "Avan." DMETS reviewed the name [redacted] in our consult 01-0090 and did not recommend the use of the name. However, we are not aware of the final outcome of our recommendation. Therefore, the name, [redacted], cannot be ignored. Although Avandamet and [redacted] a differ in dosage form, strength, and route of administration, they share similar dosing regimens. The usual dose of [redacted] and the usual dose of Avandamet is **1** tablet two to **three times daily**. Lastly, the unintentional use of Avandamet can lead to serious adverse events. Metformin in Avandamet has the following black box warning: "Lactic acidosis is rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with Avandamet; when it occurs, it is fatal in approximately 50% of cases." Rosiglitazone in Avandamet may cause unintentional hypoglycemia, especially in a patient who has baseline normal or low blood glucose levels. Symptoms associated with hypoglycemia include tachycardia, palpitations, shakiness, sweating, inability to concentrate, dizziness, hunger, blurred vision, and even impairment of motor function, seizure, or coma.

Avapro contains the active ingredient, irbesartan, and is indicated for the treatment of hypertension. Avandamet can look similar to Avapro when scripted, because they share the same beginning "Ava". However, the endings "ndamet" in Avandamet and "pro" in Avapro are different enough to distinguish the two names. Furthermore, Avanadmet and Avapro do not share overlapping strengths. Avandamet will be available in 1 mg/500 mg, 2 mg/500 mg, and 4 mg/500 mg combination strength tablets while Avapro is available only in the following single strengths: 75 mg, 150 mg, and 300 mg. We believe that the difference in the strengths will help ensure that medication errors do not occur between the two products.

Anzamet is the proprietary name for dolasetron and is used for the prevention of nausea and vomiting associated with cancer chemotherapy, the prevention of postoperative nausea and vomiting, and the treatment of postoperative nausea and/or vomiting. Both Anzamet and Avandamet sound similar due to the same beginning letter "A" and suffix "amet" in both proprietary names. However, they have different dosage forms, different strengths, and different routes of administration. Anzamet is supplied in tablets of 50 mg and 100 mg and as injection of 12.5 mg/0.625 mL and 100 mg/5 mL while Avandamet will be available as 1 mg/500 mg, 2 mg/500 mg, and 4 mg/500 mg tablets. Furthermore, Anzamet has distinctive dosing directions, and it is commonly used for the prevention of cancer chemotherapy-induced nausea and vomiting. For example, 100 mg of IV/PO Anzamet is administered prior to chemotherapy. Avanadamet, on the other hand, is dosed two to three times daily. We believe that the differences in the strengths and dosing directions will help ensure that medication errors do not occur between the two products.

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name, Avandamet, for the following reasons:

Aldomet contains the active ingredient, methyldopa, and is indicated in the management of hypertension. Aldomet is dosed 500 mg to 2000 mg daily in two to four doses. The proposed name Avandamet looks and sounds similar to Aldomet as they both begin with the letter "A" and end with similar letter combinations, "damet" and "domet" (see below). In fact, one participant from the outpatient written study interpreted the proposed name as Aldomet. We acknowledge that Avandamet contains two active ingredients and will be available as 1 mg/500 mg, 2 mg/500 mg, and 4 mg/500 mg combination strength tablets. Aldomet, on the other hand, contains one active ingredient and is available in 125 mg, 250 mg, and 500 mg single strength tablets. However, there is a similar strength (500 mg) between Avandamet and Aldomet. Furthermore, Avandamet and Aldomet share overlapping dosing intervals (BID and TID). Lastly, a prescription for "Avandamet 1 mg/500 mg TID" may be written as "Avandamet 1/500 mg TID", and this can be easily misinterpreted as "Aldomet 1 tablet of 500 mg TID". Moreover, a verbal prescription for "Avandamet 1/500 mg TID" may be heard as "Aldomet one five hundred milligram three times daily".

Avandamet 1/500 mg TID

Aldomet 500 mg TID

The inadvertent ingestion of Avandamet can result in serious toxicity. Metformin contained in Avandamet has the following black box warning: "Lactic acidosis is rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with Avandamet; when it

occurs, it is fatal in approximately 50% of cases." Furthermore, Avandamet has been associated with anemia, hypoglycemia, and diarrhea. If a patient receives Aldomet instead of Avandamet, a patient can experience various adverse events associated with antihypertensive agents, including orthostatic hypotension, bradycardia, dizziness, fatigue, and headache. Lastly, a positive Coombs test, hemolytic anemia, and liver disorders have been associated with the Aldomet therapy.

Avandia contains one of the active ingredients of Avandamet, rosiglitazone maleate. Avandia, a thiazolidinedione oral antidiabetic agent, is indicated as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes mellitus. The recommended usual starting dose is 4 mg as a single daily dose or divided and administered in the morning and evening. Avandia is available as 2 mg, 4 mg, and 8 mg tablets. Avandia and Avandamet share the same prefix "Avand". Moreover, since Avandamet also contains rosiglitazone, Avandia and Avandamet share similar strengths, "2 mg" and "4 mg". Furthermore, they share an overlapping dosing interval (BID). The strength of metformin in Avandamet differentiates these two drugs, however, all Avandamet drug products contain 500 mg of metformin: 1 mg/500 mg, 2 mg/500 mg, and 4 mg/500 mg. Therefore, a prescription for Avandamet can be ordered without the metformin strength, "500 mg." For instance, a prescription for "Avandamet 2 mg/500 mg BID" may be written as "Avandamet 2 mg BID" and this can be misinterpreted as "Avandia 2 mg BID" or vice versa (see below).

Avandamet 2mg BID #60 Avandia 2mg BID #60

Lastly, Avandamet will be placed in close proximity to Avandia on pharmacy shelves, further increasing the risk of errors. If a patient inadvertently receives Avandamet instead of Avandia, she can experience inappropriate treatment for diabetes. Furthermore, if a patient is already on metformin, she may be at an increased risk for lactic acidosis due to the additional metformin contained in Avandamet. Metformin has the following black box warning: "Lactic acidosis is rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with Avandamet; when it occurs, it is fatal in approximately 50% of cases." If a patient receives Avandia instead of Avandamet, she can experience inappropriate treatment for the existing condition due to the lack of metformin treatment in Avandia.

Additionally, DMETS has reviewed the unit dose container labels, container labels, carton and insert labeling. We have identified several areas of improvement that will minimize potential user errors.

A. UNIT DOSE LABELS

The expression of strength is not prominent and all strengths look similar. Since multiple strengths are marketed, it is important that colors, boxes, or some other means are used to distinguish each strength.

B. CARTON LABELING (100 Tablet Unit Dose)

1. See all comments under Container Label.

2. Include a statement as to whether or not the unit-dose package is child resistant.

C. CONTAINER LABEL

1. We recommend [redacted] that is incorporated in the proprietary name. It detracts attention from the proprietary name.

2. Insert a space between the number and "mg". For example, revise to read " 1 mg/500 mg" rather than ' [redacted]

3. We recommend decreasing the prominence of quantity by decreasing its font size so that it appears smaller than the strengths.

4. The Poison Prevention Packaging Act notes that special packaging (child-resistant closure) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing. Your proposed package of 60s appears to be in this category. It is not clear if the manufacturer provides the container with a child-resistant closure (CRC). Please ensure a CRC closure is being utilized.

D. PROFESSIONAL SAMPLE CARTON

See comments under Container Label.

E. PATIENT INFORMATION LABELING

No comments.

F. INSERT LABELING

No comments.

APPEARS THIS WAY
ON ORIGINAL

IV. RECOMMENDATIONS:

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

2. We recommend implementation of the labeling revisions contained in this section III of this review to minimize potential errors with the use of this product.

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.

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

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

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/s/

Hye-Joo Kim
5/10/02 10:27:48 AM
PHARMACIST

Alina Mahmud
5/10/02 12:36:17 PM
PHARMACIST

Carol Holquist
5/10/02 01:13:00 PM
PHARMACIST

Jerry Phillips
5/13/02 09:37:57 AM
DIRECTOR

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: OPDRA,
Attention: Sammie Beam, R.Ph., HFD-400

FROM: DMEDP
Jena Weber, HFD-510

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
7/24/01		N/A	Proposed trademark request	7/19/01

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
AVANDAMET	N/A	Oral hypoglycemic	10/01/01

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: See attached documentation; company is requesting FDA review and response to their proposed tradename (AVANDAMET) for the combination product rosiglitazone maleate/metformin HCl. Note that they plan on submitting their NDA in November/December 2001. No type of labeling is available at this time.

SIGNATURE OF REQUESTER: Jena M. Weber, PM	METHOD OF DELIVERY (Check one) X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

David Orloff
7/24/01 06:25:29 PM

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-410 SUPPL # N/A

Trade Name: Avandamet Generic Name: Metformin maleate & Rosiglitazone HCl

Applicant Name: GlaxoSmithKline HFD-510

Approval Date: October 10, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA? YES/_✔__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_✔__/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /___/ NO /_✔__/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Application consists of bridging of bioavailability and bioequivalence data of two clinical pharmacology studies; **study protocol 270** entitled, "A Bioequivalence Study With a Combination Tablet Formulation of Rosiglitazone and Metformin (4 mg/500 mg) Compared to Concomitant dosing of Rosiglitazone 4 mg and Metformin 500 mg Commercial Tablets and a Dose Proportionality Study Comparing the 4 mg/500 mg & 1 mg/500 mg Combination Formulations;"

and **study protocol 271** entitled, "A Study to Assess the Effect of Food on the Pharmacokinetics of a Rosiglitazone 4 mg and Metformin 500 mg Combination Tablet Formulation and a Study Comparing the Pharmacokinetics of Rosiglitazone 4 mg and Metformin 500 mg Combination Tablet to Concomitant Dosing of Rosiglitazone 4 mg and Metformin 500 mg Commercial Tablets in the Fed State in Healthy Volunteers."

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /__✔_/

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

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

NDA 21-071 Avandia (rosiglitazone maleate) WR Granted 2/1/2000
NDA 20-357 Glucophage (metformin HCl) WR Granted 6/9/99

YES /___/ NO /_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_✔__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_✔__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_✓/

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

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_✔__/ NO /___/

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

NDA # 20-357 Glucophage (metformin HCl) Tablets (AP 3/5/95)

NDA # 21-071 Avandia (rosiglitazone maleate) Tablets (AP 5/25/99)

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_✔__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /___/ NO /___/

   If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

   (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

   YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

Investigation #2	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Jena Weber
Signature of Preparer Date: 9/25/02
Title: PM

Signature of Office or Division Director Date

cc:
Archival NDA
HFD-510/Division File
HFD-510/JWeber
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

David Orloff
10/16/02 08:52:01 AM

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: August 29, 2002

To: Sharon Shapowal, R.Ph. Director, U.S. Regulatory Affairs	**From:** Jena Weber Project Manager /s/ Division of Metabolic and Endocrine Drug Products, HFD-510
Company: GlaxoSmithKline	
Fax number: 215-751-4926	**Fax number:** 301-443-9282
Phone number: 215-751-3434	**Phone number:** 301-827-6422

Subject: Discipline Review Completed for NDA 21-410; Division of Medication Errors and Technical Support – Office of Drug Safety (ODS). Reference Unit Dose Carton and Container Labels.

Total no. of pages including cover: 2

Comments: The following comments are from FDA's Office of Drug Safety. This is in response to your reply dated August 14, 2002, in which you addressed the comments and requests from ODS that appeared in our fax to you dated July 31, 2002.

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

Document to be mailed: ☐ YES ☑ NO

1. Sponsor's Response:
GSK agrees to remove the red triangle from the Avandamet logo presently shown on the Commercial Bottle Labels of 60, 100, and 500 tablets **"and the SUP Carton Label."** We propose to not delete the red triangle from the Avandamet logo on the Sample Foils and Sample Cartons, as these are promotional samples that are NOT for SALE. We have previously followed this approach with Avandia. GSK regards Avandamet as an important member of the Avandia family and in order to maintain consistency across products, we request your agreement to leave the red triangle on the Avandamet logo for the Sample Foils and Sample Carton.

DMETS Response:
We agree that the red triangle from the Avandamet logo does not have to be deleted from the sample foils and sample cartons, since these are promotional items and are "not for sale." Additionally, these promotional samples are not stocked in pharmacies to be dispensed to patients.

2. Sponsor's Response:
This (unit-dose) packaging is not child-resistant. It is not child resistant because the SUP presentation will only be prepared by the healthcare provider and distributed to the patient, a single dose at a time. It is for this reason, GSK does not consider this statement necessary on this presentation. However, GSK will include such a statement should DMETS regard it a necessary on this presentation.

DMETS Response:
DMETS originally requested that a statement be included as to whether or not the unit-dose packaging is child resistant. However, we agree that the unit-dose packaging intended only for the institutional practices, such as a nursing home or hospital, is exempt from the Poison Prevention Packaging Act. Therefore, the statement that the unit-dose package is not child-resistant is not deemed necessary on the carton labeling of the unit dose.

Additionally, DMETS has reviewed the *revised* unit dose labels, container labels, carton labeling, and have the following comment:

UNIT DOSE LABELS and CARTON LABELING (100's) (1 mg/500 mg, 2 mg/500 mg, and 4 mg/500 mg).

> Please insert a space between the number and "mg". For example, revise to read " 1 mg/500 mg" rather than '

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/s/

Jena Weber
8/30/02 07:50:33 AM

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: July 31, 2002

To: Sharon Shapowal Director, U.S. Regulatory Affairs	**From:** Jena Weber Project Manag /S/ Division of Metabolic and Endocrine Drug Products, HFD-510
Company: GlaxoSmithKline	
Fax number: 215-751-4096	**Fax number:** 301-443-9282
Phone number: 215-751-3434	**Phone number:** 301-827-6422

Subject: Discipline Review Completed for NDA 21-410; Division of Medication Errors and Technical Support – Office of Drug Safety (ODS). Reference NDA 21-410, Unit Dose, Carton, and Container Labels.

Total no. of pages including cover: 2

Comments: The Division of Medication Errors and Technical Support (DMETS) has reviewed the unit dose container labels, container labels, carton and insert labeling. They have identified several areas of improvement that will minimize potential user errors. Please address these comments and requests in writing to your NDA file for Avandamet. See attached page.

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

Document to be mailed: ☐ YES ☑ NO

A. UNIT DOSE LABELS
The expression of strength is not prominent and all strengths look similar. Since multiple strengths are marketed, it is important that colors, boxes, or some other means are used to distinguish each strength.

B. CARTON LABELING (100 Tablet Unit Dose)
1. See all comments under Container Label.
2. Include a statement as to whether or not the unit-dose package is child resistant.

C. CONTAINER LABEL
1. We recommend deleting [redacted] It detracts attention from the proprietary name.

2. Insert a space between the number and "mg". For example, revise to read " 1 mg/500 mg" rather [redacted]

3. We recommend decreasing the prominence of quantity by decreasing its font size so that it appears smaller than the strengths.

4. The Poison Prevention Packaging Act notes that special packaging (child-resistant closure) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing. Your proposed package of 60s appears to be in this category. It is not clear if the manufacturer provides the container with a child-resistant closure (CRC). Please ensure a CRC closure is being utilized.

D. PROFESSIONAL SAMPLE CARTON
See comments under Container Label.

E. PATIENT INFORMATION LABELING
No comments.

F. INSERT LABELING
No comments.

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/s/

Jena Weber
7/31/02 11:16:58 AM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-410

GlaxoSmithKline
Attention: Sharon Shapowal, R.Ph.
Director, North American Regulatory Affairs
200 North 16th Street, FP-1010
Philadelphia, PA 19102

Dear Ms. Shapowal:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Avandamet (rosiglitazone maleate and metformin hydrochloride) Tablets; 1 mg/500 mg, 2 mg/500 mg, and 4 mg/500 mg.

You were notified in our letter dated December 5, 2001, that your application was not accepted for filing due to non-payment of fees. This is to notify you that the Agency has received all fees owed and your application has been accepted as of December 10, 2001.

The review priority classification for this application is standard(S).

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 8, 2002, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be October 10, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter.

We note that you have requested a deferral of pediatric studies since no pediatric data have been included in this submission.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. We note that a written request for rosiglitazone was issued on February 1, 2000, under NDA 21-071

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-827-6422.

Sincerely,

{See appended electronic signature page}
Kati Johnson
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WA.
ON ORIGINAL

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/s/

Kati Johnson
2/8/02 07:51:32 AM

Jena Weber
2/8/02 10:35:39 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-071
NDA 21-410

GlaxoSmithKline
Attention: Sharon Shapowal
Director, Regulatory Affairs
One Franklin Plaza
Philadelphia, PA 19101

Dear Ms. Shapowal:

We acknowledge receipt on December 20, 2001 of your December 19, 2001 correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug applications (NDA):

Application number	Drug name
21-071	Avandia (rosiglitazone maleate) Tablets
21-410	Avandamet (rosiglitazone maleate & metformin HCl) Tablets

Name of New Applicant: GlaxoSmithKline

Name of Previous Applicant: SmithKline Beecham Corporation

Your correspondence provided the information necessary to effect this change and we have revised our records to indicate GlaxoSmithKline as the sponsor of record for this application.
Please note that all changes in the NDA from those described by the original owner, such as manufacturing facilities and controls, require an approved supplement before implementation.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

Please cite the NDA numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these NDAs should be addressed as follows:

U.S. Postal/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
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Jena Weber, Regulatory Project Manager, at (301) 827-6422.

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/

Kati Johnson
1/18/02 02:41:19 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-410

Glaxo SmithKline
Attention: Sharon Shapowal, R. Ph.
Director, U.S.,Regulatory Affairs
200 N. 16th Street, FP-1010
Philadelphia, PA 19102

Dear Ms. :

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:	Avandamet (rosiglitazone maleate and metformin hydrochloride) tablets; 1 mg/500 mg, 2 mg/500 mg, 4 mg/500 mg
Date of Application:	November 29, 2001
Date of Receipt:	November 29, 2001
Our Reference Number:	NDA 21-410
Applicant:	SmithKline Beecham Corporation **

We note that you are in arrears for payment of fees for products, establishments, or previously submitted applications.

Because an application is considered incomplete and cannot be accepted for filing until all fees owed have been paid, review of the application referenced above may not begin at this time. Upon receipt of the outstanding fees, we will start the user fee clock and commence review of your application. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Checks sent by a courier should be addressed to:

Food and Drug Administration (360909)
Mellon Client Service Center, Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number are on the enclosed check.

**We note that the cover letter that accompanied this submission describes *Glaxo SmithKline* as the applicant for this NDA. However, the Form FDA 365h lists the applicant as *SmithKline Beecham Corporation*. Please clarify the correct name of the applicant. If the submitted Form FDA 356h is incorrect, please submit a corrected one.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed 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, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Jena Weber, Regulatory Project Manager, at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Enid Galliers
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/

Enid Galliers
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OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information About the Submission

	Information		Information
NDA Number:	21-410	**Brand Name:**	AVANDAMET
OCPB Division (I, II, III):	DPE-II (HFD-870)	**Generic Name:**	Rosiglitazone / metformin
Clinical Division:	DMEDP (HFD-510)	**Drug Class:**	Combination
CPB Reviewer:	Steven B. Johnson, Pharm.D.	**Indication(s):**	Type 2 DM
CPB Team Leader:	Hae-Young Ahn, Ph.D.	**Dosage Form:**	Tablet
Submission Date:	29-NOV-2001	**Dosing Regimen:**	1, 2, & 4 mg + 500 mg
CPB Review Due Date:	29-JUL-2002	**Route of Administration:**	PO (oral)
Division Due Date:	29-AUG-2002	**Sponsor:**	SmithKline Beecham
PDUFA Date:	29-SEP-2002	**Priority Classification:**	Standard

Clinical Pharmacology and Biopharmaceutics Information

Information Type	"X" if included at filing	# of Studies Submitted	# of Studies Reviewed	Critical Comments (if any)
Table of Contents	X			
Tabular Listing of All Human Studies	X			
Human PK Summary	X			
Labeling	X			
Reference Bio- & Analytical Methods	X			
I. Clinical Pharmacology				
Mass Balance:				
Isozyme Characterization:				
Blood/Plasma Ratio:				
Plasma Protein Binding:				
Pharmacokinetics (PK) –				
– Healthy Volunteers –				
Single-Dose:				
Multiple-Dose:				
– Patients –				
Single-Dose:				
Multiple-Dose:				
Dose Proportionality –				
Single-Dose:	X	1		1 mg/500 mg and 4mg/500 mg
Multiple-Dose:				
Drug-Drug Interaction Studies –				
In-vivo Effects ON Primary Drug:				
In-vivo Effects OF Primary Drug:				
In-vitro Studies:				
Subpopulation Studies –				
Ethnicity:				
Sex:				
Pediatrics:				
Geriatrics:				
Renal Impairment:				
Hepatic Impairment:				
Pharmacodynamics (PD) –				
Phase 2:				
Phase 3:				
PK / PD –				
Phase 1:				
Phase 2:				
Phase 3:				
Population Analyses –				
Rich Data Set:				
Sparse Data Set:				
II. Biopharmaceutics				
Absolute Bioavailability:				
Relative Bioavailability –				
Solution as Reference				
Other Formulation as Reference:				
Bioequivalence Studies –				
– Traditional Design –				
Single-Dose:	X	1		AVANDAMET vs. Individual Components
Multiple-Dose:				

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

– Replicate Design –				
Single-Dose:				
Multiple-Dose:				
Food-Drug Interaction Studies:	X	1		
Dissolution:	X	1		
In-vitro/In-vivo Correlation:				
BCS Based Biowaiver Request:				
BCS Classification Information:				
III. Other CPB Studies				
Genotype / Phenotype Studies:				
Chronopharmacokinetics:				
Pediatric Development Plan:				
Literature References:	X	16		
TOTAL # OF STUDIES:		3 + (16)		

Filability and QBR Comments

	"X" if Yes	Comments
Is the Application Filable?	X	NONE
Comments to the Firm:		NONE
Summary		• Three strengths are proposed for evaluation: 1 mg, 2 mg, and 4 mg rosiglitazone, each in combination with 500 mg metformin hydrochloride. • A biowaiver for the two lowest strengths, 1 mg/500 mg and 2 mg/500 mg, will be sought. • Full dissolution profiles and complete formulation data are provided for each strength. • The sponsor has submitted two primary studies – one evaluating the bioequivalence of the combination 4 mg/500 mg tablet with its individual components and dose proportionality between the 4 mg/500 mg and 1 mg/500 mg tablets, and the other a food-effect comparison.
QBR Questions (*key issues to be considered*)		1) Can a biowaiver be granted for the 1mg/500 mg and 2mg/500 mg strength tablets? 2) Is the combination product bioequivalent to the individual components? 3) Has the known food-effect for the individual components been altered with this formulation?
Primary Reviewer Signature:	Steven B. Johnson, Pharm /S/	Date: 1/23/02
Secondary Reviewer Signature:	Hae-Young Ahn, Ph.D. /S/	Date: 1/23/02

– Line Listing of Studies Included in this Application –

Study #	Study Title
270	A Bioequivalence Study With a Combination Tablet Formulation of Rosiglitazone and Metformin (4 mg/500 mg) Compared to Concomitant Dosing of Rosiglitazone 4 mg and Metformin 500 mg Commercial Tablets and a Dose Proportionality Study Comparing the 4 mg/500 mg & 1 mg/500 mg Combination Formulations.
271	A Study to Assess the Effect of Food on the Pharmacokinetics of a Rosiglitazone 4 mg and Metformin 500 mg Combination Tablet Formulation and a Study Comparing the Pharmacokinetics of Rosiglitazone 4 mg and Metformin 500 mg Combination Tablet to Concomitant Dosing of Rosiglitazone 4 mg and Metformin 500 mg Commercial Tablets in the Fed State in Healthy Volunteers.

APPEARS THIS WAY
ON ORIGINAL

April 17, 2002

GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA
19101-7929

Tel. 215 715 4000
Fax. 215 751 3400
www.gsk.com

David Orloff, M.D., Division Director
Division of Metabolism and Endocrine Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
HFD-510, Document Room. 14-B-19
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-410; AVANDAMET™ (rosiglitazone maleate & metformin HCl) Tablets
Response to FDA Request/Comment:EIC of Rosiglitazone Maleate

Dear Dr. Orloff:

Reference is made to our New Drug Application to support a new formulation, a fixed-dose combination tablet, containing rosiglitazone maleate and metformin hydrochloride, NDA 21-410. The NDA was submitted on November 29, 2001, and accepted for filing December 10, 2001.

On April 15, 2002, Dr. Xavier Ysern, FDA chemist, called Mr. Justin Geiger, Senior Project Manager - NA New Submissions, requesting that we formally submit information pertaining to the categorical exclusion of Environmental Assessment requirements (EA) for rosiglitazone maleate to NDA 21-410. Specifically, Dr. Ysern asked that we provide the calculation of Expected Introduction Concentration (EIC) to support our claim that, based on the five year maximum amount of projected use, the EIC of rosiglitazone maleate is [redacted] and therefore qualifies for a categorical exclusion from EA requirements.

In accord with Dr. Ysern's request, the calculation of EIC for rosiglitazone maleate is contained herein for your review. We respecfully remind the Agency that the enclosed information is considered proprietary and therefore should not be made available to the public domain via FOI.

3.E Preclinical Summary

Note to Reviewer:

Available by cross-reference only to NDA 21-071, approved May 25, 1999.

MEMORANDUM

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

DATE: October 10, 2002

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

TO: NDA 21-410
Avandamet (rosiglitazone maleate and metformin)
Glaxo-SmithKline
Treatment of type 2 diabetes mellitus

SUBJECT: NDA review issues and recommended action

Background
The combined use of rosiglitazone (RZG) and metformin (MET) was previously approved (1999) for use in patients inadequately controlled on metformin alone. Avandia is to be added to rather than substituted for a maximum dose of metformin. The study supporting the combination showed an incremental approximate 1% lowering of HbA1c when RZG as added to MET versus remaining on MET alone. Patients who were switched from MET to RZG showed deterioration in glycemic control.

Clinical
No new studies of clinical safety and efficacy were performed to support the current application. The labeling has been reviewed by the clinical team and it is acceptable.

Biopharmaceutics
The approval of this application relies on the establishment of bioequivalence for RZG and MET between the combination product and each component given separately but simultaneously. This has been established and dose-proportionality was established between the 1/500 and 4/500 dosage strengths.

OCPB has accepted final labeling and the sponsor has addressed concerns by OCPB re: dissolution specifications as discussed in Dr. S. Johnson's review.

Labeling
The labeling for Avandamet is consistent with the labeling for Avandia and metformin. The indication for the use of Avandamet follows from the indications for combination therapy in the RZG label. It is indicated for patients inadequately controlled on metformin alone or in those already treated with both medications. Dosage recommendations are consistent with the labels for metformin and RZG.

Pharmacology/Toxicology
No new toxicology studies were conducted.
Chemistry/ Microbiology
The chemistry, manufacturing, and controls are satisfactory and the application is approvable from the standpoint of ONDC. No deficiencies were identified.
The manufacturing site inspections were all acceptable.
A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

DSI/Data Integrity
The 2 bioequivalence studies were audited by DSI. The recommendation was that the clinical portions of the studies were acceptable for review and that the analytical portions were problematic because of issues related to documentation of bench-top and — stability of metformin in plasma. Dr. Johnson has addressed this in his review and there is no impact on his recommendation for approval.

Financial disclosure
The financial disclosure information is in order. The sponsor has certified that no investigator received outcome payments, that no investigator disclosed a proprietary interest in the product or an equity interest in the company, and that no investigator was the recipient of significant payments of other sorts.

ODS/nomenclature
DMETS recommended against Avandamet as a tradename citing potential medication errors with Aldomet. The annual prescriptions of Aldomet are extremely small and it is therefore unlikely that most pharmacies will even have Aldomet on the shelves. Furthermore, since the use of Avandamet is in patients inadequately treated with metformin or already on metformin and Avandia, pharmacists will likely recognize what amounts to a simple transition in patients' diabetes medications. The division has accepted the proposed tradename.

Pediatric issues
A deferral has been granted for pediatric studies until data are available with RZG monotherapy in children with type 2 diabetes.

Recommendation
The application may be approved.

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/s/

David Orloff
10/10/02 07:20:32 PM
MEDICAL OFFICER