CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-410

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW
Physician Insert Labeling Review

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: NDA 21410
Sponsor: GlaxoSmithKline
Date of Submission: 12/10/01

Application Type: NDA (505b1)
Proprietary Name: AVANDAMET
Generic Name: Rosiglitazone/metformin

Pharmaceutical Category: Combination Anti-diabetic Agent
Thiazolidinedione (rosiglitazone) + Biguanide (metformin)
(3031400)

Route of Administration: oral

Indication: Treatment of Type 2 Diabetes Mellitus

Dosage: 1/500 mg, 2/500 mg, 4/500 mg

Reviewer: Joanna K. Zawadzki, M.D.

Date Review Completed: 9/16/02

Chemistry Reviewer: Yavier Ysern, Ph.D.

Biopharmaceutics Reviewer: Steven B. Johnson, Pharm.D.

Project Manager: Jena Weber

LABELING REVIEW SUMMARY:

NDA 21-410 consists of an application for the fixed-dose combination tablets of rosiglitazone maleate and metformin hydrochloride (AVANDAMET) for the treatment of type 2 diabetes mellitus. This application was through the bioequivalency route, and additional clinical studies were not submitted. The labeling implications of this submission are summarized in this review.

OUTSTANDING ISSUES:
Comments to the sponsor regarding the general readability of the label, the specific indication for AVANDAMET, and unbalanced emphasis on the respective rosiglitazone and metformin labels should be forwarded to the sponsor. The specific comments to the sponsor were discussed in the Division labeling meeting on 9/19/02. The amended label that was forwarded to the sponsor is attached to this document.

RECOMMENDED REGULATORY ACTION: N drive location:

NDA, Efficacy/Label supplement: _____ **Approvable** _____ **Not Approvable**
_____x___ **Approve with labeling changes**

SIGNATURES:

Medical Reviewer: Joanna K. Zawadzki, M.D. **Date:** 9/19/02

Medical Team Leader: David G. Orloff, M.D. **Date:** _____
and
Division Director:

Summary of NDA Application

NDA 21-410 consists of an application for the fixed-dose combination tablets of rosiglitazone maleate and metformin hydrochloride (AVANDAMET) for the treatment of type 2 diabetes mellitus. The combined use of rosiglitazone maleate (AVANDIA) and metformin hydrochloride was approved for the treatment of type 2 diabetes mellitus by the FDA on 5/25/99 on the basis of two clinical trials, at the same time as rosiglitazone monotherapy was initially approved (NDA 21-071). The approval of combination rosiglitazone and metformin therapy was based on two clinical trials in which rosiglitazone was added to maximal metformin therapy. There were no clinical trials in NDA 21-071 in which combination therapy was initiated in patients who were naïve to pharmacologic therapy for type 2 diabetes mellitus. The design of these two clinical trials is summarized below: (excerpted from statistical review by J. Mele, M.S.,);

The sponsor had conducted two 26-week trials (Table22) [in NDA 21-071] to assess the efficacy and safety of rosiglitazone in combination with metformin for patients considered inadequately controlled on metformin (140≤FPG≤300). For Study 093, rosiglitazone 4 mg BID was combined with metformin and for Study 094, rosiglitazone 4 mg OD and rosiglitazone 8 mg OD were each combined with metformin.

Table 22. Combination with Metformin Trials

	# of Sites	Treatment Arms (N)	Duration of Treatment
093 (6/97 to 4/98)	34 (USA)	RSG 4 mg BID+Met (106) RSG 4 mg BID+Plac (107) Metformin+Placebo (109)	3 weeks titration to Met 2.5 mg 4 weeks Metformin 2.5 mg+diet 26 weeks rand. treatment
094 (4/97 to 3/98)	36 (USA)	RSG 4 mg OD+Met (119) RSG 8 mg OD+Met (113) Metformin+Placebo (116)	3 weeks titration to Met 2.5 mg 4 weeks Metformin 2.5 mg+diet 26 weeks rand. treatment

The application for AVANDAMET [NDA 21-410] is based on two clinical pharmacology studies (a bioequivalence/dose proportionality study (270) and a food-effect study (271) and, by cross-reference, on the efficacy and safety data previously submitted in support of NDA 21-071. No additional clinical studies were submitted with this NDA. As a 505b2 application, the review and recommendation for approval of this application is based on bioequivalence and is done primarily by the Clinical Pharmacology and Biopharmaceutics Team. The clinical pharmacology reviewer (S. B. Johnson, Pharm.D.) concluded that bioequivalence was achieved between the 4mg/500 mg AVANDAMET tablets and the respective components, for both AUC and Cmax parameters, and dose proportionality was established between the 1 mg/500 mg and 4 mg/500 mg AVANDAMET tablets. No food-effect difference was noted between AVANDAMET and rosiglitazone and metformin administered concomitantly, under high fat conditions. A biowaiver for the 2 mg/500 mg dose was recommended on the basis of proportional formulations, *in-vivo* dose-proportionality between 2 of the 3 strengths, and similar dissolution profiles. Thus this fixed combination tablet of rosiglitazone and metformin (AVANDAMET) would represent a convenience for the patient requiring combination rosiglitazone and metformin therapy.

Labeling Comments

Labeling was discussed during the Clinical Pharmacology and Biopharmaceutics Team meeting (8/30/02), and the following comments summarize the major clinical issues in that discussion as well as some specific comments..

The physician label is a compilation of the comments in the individual labels of rosiglitazone and metformin, with comments about each drug component under each section of the label. A similar format was also used in the physician label for Glucovance, fixed combination tablets of glyburide and metformin (NDA 21-178, approved 7/31/00). However, Glucovance was approved for both initial and secondary treatment of type 2 diabetes on the basis of clinical trials in both pharmacologically naïve and combination-treated patients. Thus the label is very extensive, complex, and not easily readable. A longer summary about this combination drug and the indication at the beginning of the physician label may help to guide the reader. There is a greater emphasis about the efficacy and adverse events relating to rosiglitazone than to metformin monotherapy. For consistency, the greatest emphasis should be on combination rosiglitazone and metformin therapy, with references to the physician labels for rosiglitazone and metformin therapy.

The sponsor's indication for the treatment of type 2 diabetes mellitus is broad and does not differentiate between patients on combination rosiglitazone and metformin therapy, patients who have failed metformin or rosiglitazone monotherapy, and patients who are naïve to pharmacologic therapy for type 2 diabetes mellitus. Based on NDA 21-410, AVANDAMET is indicated for patients previously treated with combination rosiglitazone and metformin, but AVANDAMET has not been clinically evaluated in patients previously treated with just diet and exercise, or only rosiglitazone or metformin monotherapy. Thus the NDA does not support the latter indications, and the information should be included in the label. Ideally, the sponsor should be encouraged to study the broader indications in clinical trials. If clinicians choose to prescribe AVANDAMET for the broader indications, they need to be aware of the limitations of the available data so that they can proceed appropriately cautiously.

The following labeling recommendations also include responses to the following comments suggested by the reviewer in DDMAC (M. Kiester, Pharm.D., memorandum 6/02):

1) Clinical Pharmacology section: -Avandamet combines two antidiabetic agents with ——— mechanisms of action to improve glycemie control in patients with type 2 diabetes."
   - This statement is ———

2) Clinical Pharmacology section: „Rosiglitazone, a member of the thiazolidinedione class of antidiabetic agents, improves glycemic control by improving insulin sensitivity while reducing circulating insulin levels."
   - The Avandia PI does not include the part about reducing circulating insulin levels. Is this necessary here?

3) Clinical Studies: The second paragraph in this section is —— . Monotherapy results with metformin are not discussed. Is it necessary to discuss monotherapy results with

rosiglitazone?

4) Warnings: The Warnings section does not include the following risk information from the Avandia PI:
"Avandia is not recommended in patients with NYHA class 3 and 4 cardiac status."

5) Adverse Reactions: The adverse reactions section includes only the rates of adverse events from the rosiglitazone trials. However, these rates are lower than those listed in the Glueophage PI. The rates of GI events in particular are much higher in the Glucophage PI than the Avandamet PI or the Avandia PI. Is it possible to include some of these rates in the Avandamet PI?

Number of Pages Redacted 2

❖❖❖

Draft Labeling
(not releasable

3.G Clinical Data Summary

Note to Reviewer:

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

NDA 21-410
Avandamet (rosiglitazone maleate & metformin HCl)
GSK

This application did not require a review by Biometrics.

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Request for Pediatric Deferral

Application #: NDA 21410
Sponsor: GlaxoSmithKline
Dates of Submission: 12/10/01
7/19/01 (pediatric deferral)
Pharmaceutical Category: Combination Anti-diabetic Agent
Thiazolidinedione (rosiglitazone) + Biguanide (metformin)
(3031400)
Indication: Treatment of Type 2 Diabetes Mellitus
Reviewer: **Joanna K. Zawadzki, M.D.**

Application Type: NDA
Proprietary Name: AVANDAMET
Generic Name: Rosiglitazone/metformin
Route of Administration:
oral
Dosage: 1/500 mg, 2/500 mg, 4/500 mg
Date Review Completed: 9/26/02

Chemistry Reviewer: Yavier Ysern, Ph.D.

Biopharmaceutics Reviewer: Steven B. Johnson, Pharm.D.

Project Manager: Jena Weber

SUMMARY:

NDA 21-410 consists of an application for the fixed-dose combination tablets of rosiglitazone maleate and metformin hydrochloride (AVANDAMET) for the treatment of type 2 diabetes mellitus. This application was submitted through the bioequivalency route, and additional clinical studies were not submitted. The sponsor had previously (7/19/01) submitted a request for deferral of pediatric studies. This request was based on the status of the individual drugs: metformin and rosiglitazone. Whereas metformin has been approved for use in the treatment of type 2 diabetes mellitus in pediatric patients aged 10-16 years (approval 12/15/00), [redacted] Protocol 49653/207 is the ongoing clinical study designed to evaluate safety and effectiveness of rosiglitazone (Avandia) in pediatric patients. Enrollment has been slow in this study, partly perhaps because of the low prevalence of type 2 diabetes mellitus in the pediatric population. The sponsor had requested the deferral of pediatric studies with AVANDAMET until after the approval of the AVANDAMET NDA and the availability of the pediatric rosiglitazone monotherapy data.

RECOMMENDATION: Pediatric Deferral

This deferral for pediatric studies with AVANDAMET will be reevaluated after the pediatric rosiglitazone data are available for review.

RECOMMENDED REGULATORY ACTION: N drive location:

NDA, Efficacy/Label supplement: _____ **Approvable** _____ **Not Approvable**
__x__ **Approve with labeling changes**

Pediatric Deferral Granted: x

SIGNATURES:

Medical Reviewer: Joanna K. Zawadzki, M.D. **Date:** 9/26/02

Medical Team Leader: David G. Orloff, M.D. **Date:** _____
and
Division Director:

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

/s/

Joanna Zawadzki
9/26/02 03:43:58 PM
MEDICAL OFFICER

David Orloff
10/2/02 06:55:21 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Attachment 1

Proposed trademark: AVANDAMET

GlaxoSmithKline conducted a full trademark search for AVANDAMET in the US, including trademarks filed with the US Patent & Trademark Office and pharmaceutical trademarks in use in the US listed in the *2001 Physician's Desk Reference*, *2001 Drug Topics Redbook* and *American Drug Index 2000*. The full trademark search did not disclose any trademarks that appear to be substantially similar to AVANDAMET. We request that DMEDP consider this name and communicate agreement or objection as early as possible to the sponsor. Further, we understand that the Office of Postmarketing Drug Risk Assessment (OPDRA) must review or be consulted on product nomenclature, and request that AVANDAMET be forwarded to their attention.

Compound number assigned: SB-712753

GSK has assigned SB-712753 to rosiglitazone maleate/metformin HCl tablets in the strengths of 1 mg/500 mg, 2 mg/500 mg and 4 mg/500 mg, rosiglitazone/metformin HCl. This number will begin to appear in AVANDAMET reports and documents. Please note that BRL-49653C (rosiglitazone maleate) may still appear on documents for AVANDAMET.

Request for Deferral of Pediatric Studies

While metformin HCl (Glucophage®, Bristol-Myers Squibb) has been approved for use in the treatment of type 2 diabetes mellitus in pediatric patients aged 10-16 years (ref. approval of December 15, 2000), Protocol 49653/207 is the ongoing clinical study designed to evaluate the safety and effectiveness of *Avandia* as monotherapy in pediatric patients. The prevalence of type 2 diabetes in children is still low and this study is progressing slowly. Nevertheless, once data from 49653/207 have been analyzed, and the safety and effectiveness of rosiglitazone monotherapy defined in the population, GSK will then be able to determine with DMEDP the best course for further studies in pediatric patients with combination therapy. GSK herein requests deferral of pediatric studies with AVANDAMET until after approval of the NDA and until after the rosiglitazone monotherapy data are available. We appreciate your consideration of this request.

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA: 21-410 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

mp Date: November 29, 2001 Action Date: October 10, 2002

...D-510 Trade and generic names/dosage form: Avandamet (rosiglitazone & metformin)

Applicant: GlaxoSmithKline Therapeutic Class: 4 S

Indication(s) previously approved: As an adjunct to diet and exercise for use in patients with Type 2 Diabetes Mellitus.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: see above

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

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for deferral:

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

Other:_____

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

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

Section D: Completed Studies

Age/weight range of completed studies:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Comments:

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

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

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

Indication #2: _____

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

- ☐ **Yes: Please proceed to Section A.**

- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

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

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

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
revised 1-18-02)

QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337