CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-071/001

CORRESPONDENCE

FAX MESSAGE

TO	**Jena Weber**	FAX NUMBER	**301-443-9282**
DATE	**13 July 1999**	TOTAL PAGES	**1**
FROM	**Sharon Shapowal**	FAX NUMBER	**215-751-4926**
TELEPHONE	**610-917-5907 (alt. 215-751-3524)**	MAILCODE	

Message/Special Instructions:
Jena: As we discussed today regarding financial disclosure and 21-071/S-001 (*Avandia* in combination with sulfonylurea therapy)

The efficacy and safety data for the pivotal studies of this supplement were provided in the original application, submitted on November 24, 1998. There was considerable discussion between SB and FDA regarding whether the original application (initial approval) would cover two indications (i.e. monotherapy and combination with metformin) or three indications (i.e. monotherapy, combination with metformin, and combination with SU). In an effort to expedite the review, as rosiglitazone NDA had been placed on a 6-month review clock, SB and FDA agreed that while all safety data for the SU studies would be incorporated into the initial approval, the efficacy data could be reviewed separately in an efficacy supplement post-approval. Nevertheless, all efficacy data files (as electronic data sets) were submitted to the initial NDA of November 24, 1998. Thus, all pivotal data for *Avandia* in combination with SU were submitted prior to the February 2, 1999 final rule date for financial disclosure.

We believe that the submission of June 2, 1999 is technically a re-submission of efficacy and safety data for the SU combination already provided to FDA. In fact, all safety data are by cross-reference only.

SmithKline Beecham would appreciate re-consideration of the requirement for financial disclosure information for S-001. As this is a potential 'refuse to file' issue, we are very concerned that SB and FDA come to resolution quickly. Thank you for handling as expeditiously as possible.

Kind regards, Sharon

FAX MESSAGE

301-827-0878

TO	Ms. Jena Weber	FAX NUMBER	~~301-443-9282~~
DATE	29 March 2000	TOTAL PAGES	24
FROM	Ms. Sharon Shapowal	FAX NUMBER	215-751-4096
TELEPHONE	215-751-3434 / 610-917-6365	MAILCODE	

Message/Special Instructions:

Dear Jena: This label incorporates all revisions to the existing *Avandia* label (AV:L2) up to the changes sent by fax, yesterday, in connection with S-001. It is easiest to read, sometimes, in context.

As noted this morning, the symbol "≥", while OK in the electronic document, was printing as a "•" in certain spots. We will assure that that is taken care of today. Also, we inserted "a" in front of "sulfonylurea" in a couple of spots for ease of reading.

I'll be back in town this afternoon, but Susan Weill (ext. 3440) is on alert if you need anything this morning.

Talk to you soon & regards, Sharon

APPEARS THIS WAY
ON ORIGINAL

FOR NDA 21-071/S-001 – these comments are from the statistical reviewer and the medical officer. These 2 pages were sent (fax) to SKB (Sharon Shapowal) on 3/27/00.

- I have the following suggestions regarding the first 2 paragraphs on page 12 of the Avandia label submitted 2/17/00.

1. For the first paragraph, the following changes in bold and italics are recommended.

2. Add back Table 5 and make the following changes:

- Eliminate the [redacted] under HbA1c in Table 5 for both studies. This percentage was not an endpoint in this study.
- Put a plus sign in front of increases from baseline.
- Report means not medians for HbA1c for Study D.
- Eliminate the middle column of data [redacted]

3. For the second paragraph describing the third study (Study 079), the following changes in bold and italics are recommended.

Medical officer
CBE changes

Labeling Issues to be communicated to SKB

PD: change _____ to "additive".

Indications: The language for metformin and SFU are similar. It would be preferable to combine the indications as follows:
" Avandia is indicated for use in combination with metformin or SFU's when diet, exercise etc.....Avandia should be added to rather than substituted for, metformin or SFU's."

Dosage and Administration: _____ A sentence should be added to warn physicians to lower the dose of SFU in case of hypoglycemia. This appears in the Actos label and should be in the Avandia label as well.

Liver toxicity and congestive heart failure: the text should be updated to reflect post-marketing reports.

MEMORANDUM OF MEETING

Meeting Date: Wednesday August 4, 1999; @ 3:30 pm, Room 1456

Application: SKB application for Avandia (rosiglitazone) NDA 21-071/S-001

Type of Meeting: Filing meeting

Meeting Recorder and Chair: Jena Weber, CSO

FDA Attendees

Solomon Sobel, M.D.	Division Director
Robert Misbin, M.D.	Medical Officer
Saul Malozowski, M.D.	Team Leader, Medical Officer
Joy Mele, M.S.	Statistician
Robert Shore, Pharm.D.	Biopharmaceutics
Roy Blay	DSI
Jena Weber	RHPM

Meeting Objectives: To determine if this supplement is fileable, priority or standard review, advisory committee needed.

Comments:

Pharmacology/Toxicology:	No issues, no relevant material submitted for review.
Biopharmacology:	No issues, no relevant material submitted for review.
Chemistry (CMC):	No issues, no relevant material submitted for review.
Statistics:	No issues, will need hard copies appropriate volumes of NDA; filable.
MO:	No issues, filable.
DSI:	Inspection just recently done; may or may not inspect. Could co-ordinate with inspection of the insulin supplement that will be submitted shortly, if sites are overlapping.

Conclusions:

1. Application is **fileable.**
2. Submission will be assigned **Standard review** status.
3. No Advisory Committee will be required.

cc: NDA 21-071
HFD-510/Div. Files
HFD-510/Meeting Minutes files
HFD-511/JWeber
HFD-510/SSobel/RMisbin/SMalozowski/HYAhn/RShore/XYsern/SMoore/JMele/TSahlroot
Hrhee/RSteigerwalt
HFD-344/RBlay

Drafted by:Jweber 8/16/99

cc: Rmisbin 10/8/SMalozowski 10/8/JMele 10/12/RShore 10/13/99
Final: Jweber 10/12/99

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

JUN 21 1999

NDA 21-071/S-001

SmithKline Beecham Pharmaceuticals
Attention: Sharon W. Shapowal, R.Ph.
Associate Director, U.S. Regulatory Affairs
1250 South Collegeville Road
Mail Code UP4305, P.O. Box 5089
Collegeville, PA 19426-0989

Dear Ms. Shapowal:

We acknowledge receipt of your efficacy supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Avandia® (rosiglitazone mateate) Tablets
NDA Number:	21-071
Supplement Number:	S-001
Therapeutic Classification:	Standard (S)
Date of Supplement:	June 2, 1999
Date of Receipt:	June 3, 1999

Unless we notify you within 60 days of our receipt 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 August 2, 1999 in accordance with 21 CFR 314.101(a).

On February 2, 1998, FDA published a final rule requiring applicants of drug, biological or device marketing applications to submit certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies covered by the rule. On December 31, 1998, an amendment to the February 1998 rule was published. The requirement became effective February 2, 1999. The rule is intended to ensure that financial interests and arrangements of clinical investigators that could affect reliability of data submitted to FDA in support of product marketing are identified and disclosed by the sponsor of any drug, biological product or device marketing application. The regulations for this rule are at 21 CFR Part 54 and 21 CFR Part 314.

Under this regulation, an applicant is required to submit to FDA a list of clinical investigators who conducted covered clinical studies and to make one of two submissions:

1. Certification that no financial arrangements with an investigator have been made where outcome affects compensation (also that the investigator has no proprietary interests in the tested product, significant equity interest or any significant payments of other sorts) or

2. Disclosure of specified financial arrangements and how applicants are managing the potential for bias. Disclosable financial arrangements include:

   a. compensation made to the investigator in which the value of compensation could be affected by study outcome for all covered studies whether ongoing or completed;

   b. a proprietary interest in the tested product, including but not limited to, a patent, trademark, copyright or licensing agreement. This requirement applies to all covered studies, whether ongoing or completed;

   c. any equity interest in the sponsor of a covered study, i.e., any ownership, stock options, or other financial interest whose value cannot be readily determined through reference to public prices for all covered studies, whether ongoing or completed. Any equity interest in a publicly held company that exceeds $50,000 in value must be disclosed for those covered clinical trials that are ongoing as of February 2, 1999, during the time the clinical investigator is carrying out the study and for one year following completion of the study; and

   d. significant payments of other sorts, meaning payments made on or after February 2, 1999, to the investigator or institution to support investigator activities that have a monetary value of more than $25,000, exclusive of the costs of conducting the study or other clinical studies (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for one year following the completion of the study.

Please refer to points 1 or 2 above and indicate the appropriate area for your clinical investigators.

Further, 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 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study 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 will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

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. If you wish to qualify for pediatric exclusivity, you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

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

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, MD 20857

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

Sincerely,

/S/ for

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

SB

SmithKline Beecham
Pharmaceuticals

FDA SUPP AMEND

S&1-001
BM

March 2, 2000

Avandia™ (rosiglitazone maleate) Tablets
NDA 21-071/S-001

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR - 9 2000
HFD-510

Mr. Roy Blay
Clinical Investigations Branch
HFD-344
Metro Park North 1, Room 125
7520 Standish Place
Rockville, MD 20855

REVIEWS COMPLETED	
CSO ACTION:	
☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

noted
/S/
3/9/00

Response to FDA Request for Information

Dear Mr. Blay:

Reference is made to our supplemental New Drug Application for the anti-diabetic compound, Avandia® (rosiglitazone maleate), sNDA 21-071/S-001 (***Avandia* in combination with sulfonylurea**), submitted June 3, 1999. Further reference is made to communications with the Agency on October 29 and November 2 and 4, 1999 in which you requested investigator, patient, and protocol information from our pivotal U.S. studies for this indication (079 and 096). The supporting details were provided in a submission dated November 10, 1999.

SB was also requested to submit, at a future date, monitoring information in tabular format for studies 079 and 096. This is being provided in the following requested format:

- column 1: Protocol number;
- column 2: Site/Center number;
- column 3: Name and address of the principal investigator and site;
- column 4: Name and address of the monitoring organization and type (e.g. CRO);
- column 5: Name of the monitor and dates of monitoring responsibility;
- column 6: "Yes/No" answer regarding whether original subject documents were reviewed during the monitoring visit;

In addition, a copy of the monitoring SOP (standard operating procedure) used at each site is enclosed for your review. We confirm that all monitors involved with these studies were to be

using the SmithKline Beecham SOPs supplied herein. Two copies of this submission are also being sent to the DMEDP Document Control room at HFD-510.

If you have any questions or requests regarding these data, please do not hesitate to contact me by phone at (215) 751-3434 or by fax at (215) 751-4096.

Sincerely,

Sharon W. Shapowal

Sharon W. Shapowal, R.Ph.
Director
U.S. Regulatory Affairs

Desk Copy: Ms. J. Weber (HFD-510)

APPEARS THIS WAY
ON ORIGINAL

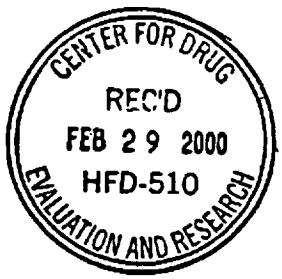
SmithKline Beecham
Pharmaceuticals

ORIGINAL

NDA SUPP AMEND
S-001 SD

Avandia® (rosiglitazone maleate)
21-071/S-001

February 25, 2000



John Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Amendment to Pending sNDA – Safety Update

Dear Dr. Jenkins:

Reference is made to our supplemental New Drug Application for the anti-diabetic compound, Avandia® (rosiglitazone maleate), sNDA 21-071/S-001 (***Avandia* in combination with sulfonylurea**), submitted June 3, 1999. Further reference is made to the request of medical officer, Dr. Robert Misbin (ref. conversation of January 28, 2000) for a safety update to the application.

Submitted herewith, in duplicate, is the safety update, which includes both clinical trials data and postmarketing surveillance data, as requested. In addition, the clinical trials safety update encompasses the monotherapy and combination with metformin studies (current approved indications for *Avandia*), as well as the sulfonylurea studies. With respect to hepatic safety data, data from clinical studies across indications has been included, as delineated in the facsimile of February 3, 2000 (See Item 19 – Other, of this submission).

APPEARS THIS WAY
ON ORIGINAL

One Franklin Plaza, PO Box 7929, Philadelphia, PA 19101. Telephone (215) 751 4000. Fax (215) 751 3400.

You will note that the clinical trials data herein provided represent a 37% increase in patient years of exposure to rosiglitazone, either as monotherapy or in combination with metformin or sulfonylurea, over the last safety update to the original NDA. More than 2500 patients having been treated for one year or more, and approximately 1000 patients having been treated for 2 years or more with rosiglitazone in clinical trials. The liver safety profile has not changed since NDA approval in May 1999. The 7.5 months of postmarketing surveillance data herein provided (against a background of more than 350,000 patients exposed in the U.S.) corroborate the safety profile defined by the clinical trials experience, inclusive of profile of hepatic safety. If this current profile of hepatic safety with *Avandia* is maintained through at least one year of commercial experience, SmithKline Beecham may wish to revisit with the Agency the necessity/frequency of liver monitoring with this product.

Please do not hesitate to contact me at 215-751-3434 (phone) or 215-751-4096 (fax) with comments or questions on this matter.

Sincerely,

Sharon W. Shapowal

Sharon W. Shapowal, R.Ph.
Director, *Avandia*
U.S. Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION
LETTER N.A.I. MEMO
CSO INITIALS DATE

Desk copy: Ms. J. Weber

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

SmithKline Beecham
Pharmaceuticals

NDA SUPP AMEND
SE1-001-BM

Avandia® (rosiglitazone maleate)
Amendment to pending sNDA 21-071/S-001

February 21, 2000

John Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Amendment: Response to FDA Request for Information

Dear Dr. Jenkins:

Reference is made to our supplemental New Drug Application for the anti-diabetic compound, Avandia® (rosiglitazone maleate), sNDA 21-071/S-001 (*Avandia* in combination with sulfonylurea), submitted June 3, 1999. Further reference is made to a fax received February 18, 2000 from Ms. Jena Weber for Dr. Misbin requesting 7 illustrations from sNDA 21-071/S-001 (i.e. tables and figures). Dr. Misbin requested these illustrations in a format, and downloaded to diskette, so that he might be able be incorporate them directly into his review.

Submitted herewith, in duplicate, are the requested illustrations as extracted from the sNDA. They have been loaded to diskette (in Microsoft Word), and printed in hard copy for reference.

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
DATE

Please note that Dr. Misbin also requested for Study '096' that the dose of glyburide for each study arm be provided. Because this cut of the data is not immediately available electronically, we will need some extra time to fulfill this part of the request. Thank you for your patience.

Please do not hesitate to contact me at 215-751-3434 (phone) or 215-751-4096 (fax) with comments or questions on this matter.

Sincerely,

Sharon W. Shapowal, R.Ph.
Director, *Avandia*
U.S. Regulatory Affairs

Desk copy: Ms. J. Weber

APPEARS THIS WAY
ON ORIGINAL

SmithKline Beecham
Pharmaceuticals

DUPLICATE

Avandia® (rosiglitazone maleate)
21-071/S-001

NDA SUPP AMEND
SE1-001-BL

February 17, 2000

John Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Amendment to Pending sNDA

Dear Dr. Jenkins:

Reference is made to our supplemental New Drug Application for the anti-diabetic compound, Avandia® (rosiglitazone maleate), sNDA 21-071/S-001 (***Avandia* in combination with sulfonylurea**), submitted June 3, 1999. Further reference is made to two brief telephone conversations with the Agency on October 8, 1999 and January 28, 2000, during which we notified the review division of our intent to revise the pending draft label.

Submitted herewith, in duplicate, is the revised *Avandia*® prescribing information for combination with sulfonylurea (both draft annotated and draft non-annotated or "clean" copy). Also enclosed is a diskette containing the clean copy of the revised label. Please note that this label supercedes the proposed draft *Avandia* label submitted on June 3, 1999.

In November 1999, the commercial *Avandia* label was revised to add a paragraph under the *Edema* subsection of PRECAUTIONS. The label herein submitted reflects this additional text. Also, SB elected to reduce the amount of descriptive text regarding the sulfonylurea clinical trials, which had added considerably to length of the draft label. Finally, the "Dosage and Administration" section was revised to be clearer to the prescriber.

000001

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989. Telephone (610) 917 7000. Fax (610) 917 7707.

At this time, we are also amending the pending sNDA to update the patent information and to appropriately reflect the corporation's ownership of *Avandia*.

Please do not hesitate to contact me at 215-751-3434 (phone) or 215-751-4096 (fax) with comments or questions on this matter.

Sincerely,

Sharon W. Shapowal, R.Ph.
Director, *Avandia*
U.S. Regulatory Affairs

Desk copy: Ms. J. Weber

APPEARS THIS WAY
ON ORIGINAL

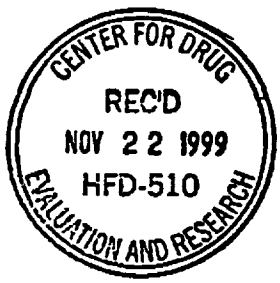
ORIGINAL

SmithKline Beecham
Pharmaceuticals

SE1-001-BM

November 10, 1999

NDA 21-071 (S-001)
Avandia® (rosiglitazone maleate) Tablets
Volumes 1 - 8



Solomon Sobel, M.D., Division Director
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products (HFD-510)
Document Control 14B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Response to FDA Request for Information

Dear Dr. Sobel:

Reference is made to our supplemental New Drug Application for Avandia® (rosiglitazone maleate) Tablets, NDA 21-071 (S-001) for the treatment of type 2 diabetes mellitus in combination with sulfonylurea, submitted on June 3, 1999. Additional reference is made to communications on October 29 and November 2 and 4, 1999 with Dr. Hsien Ju of the Clinical Investigations Branch (HFD-46) in which he requested and we provided investigator and patient information from our three pivotal studies (015, 079 and 096) supporting this supplemental NDA.

In response to Dr. Ju's November request, we are providing additional information for the following investigator study sites:

Study 079:	Dr. Herron (Ctr 003), Chicago, IL
	Dr. Rendell (Ctr 024) Omaha, NE-
Study 096	Dr. Kipnes (Ctr 013), San Antonio, TX
	Dr. Spisak (Ctr 019), Portland, OR

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

Attached for each study is a 1572 form, a copy of the protocol and amendments, a summary of patient disposition, a list of discontinuations and the reason(s) for withdrawal, a list of adverse

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989. Telephone (610) 917 7000. Fax (610) 917 7707.

events for all patients at these sites, a list of protocol violations, and the identified case report forms. A Table of Contents for this submission is attached following this letter.

Please contact me at (610) 917-5302 via phone or (610) 917-7665 via facsimile should you have any questions regarding this submission.

Sincerely yours,

Matthew Whitman
Manager
U.S. Regulatory Affairs

Desk Copy: H.W. Ju, M.D.; HFD-46 (Sent under separate cover)

APPEARS THIS WAY
ON ORIGINAL

SUPPL NEW CORRESP
SE1-001-SNC

SmithKline Beecham
Pharmaceuticals

DUPLICATE

August 16, 1999

Avandia® (rosiglitazone maleate) Tablets
NDA 21-071/S-001

Solomon Sobel, M.D., Division Director
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products (HFD-510)
Document Control 14B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Amendment: FDA request for official correspondence (financial disclosure)

Dear Dr. Sobel:

Reference is made to our New Drug Application for Avandia® (rosiglitazone maleate) Tablets, NDA 21-071/S-001, submitted on June 2, 1999 for the treatment of Type 2 diabetes mellitus in combination with sulfonylurea (SU) therapy. Additional reference is made to a July 13, 1999 conversation with and facsimile to Ms. Jena Weber, and to a telephone conversation on August 5, 1999, to discuss the financial disclosure requirement as it applies to studies completed prior to February 2, 1999.

On August 5, 1999 Ms. Weber informed SB that the supplemental NDA for the indication of *Avandia* in combination with sulfonylurea for the treatment of type 2 diabetes mellitus had been deemed filable at the Division's meeting of August 4, 1999. Financial disclosure information had not been raised as a specific issue. SmithKline Beecham believes that for the reasons stated below, and previously discussed by telephone and outlined in the facsimile, financial disclosure for S-001 is not required. Ms. Weber requested that we address the issue officially to the file.

Historical perspective: As previously discussed, the efficacy and safety data for the pivotal studies of this supplement were provided in the original new drug application for *Avandia*, submitted on November 24, 1998. There was

1250 S. Collegeville Road. PO Box 5089. Collegeville, PA 19426-0989. Telephone (610) 917 7000. Fax (610) 917 7707.

considerable discussion between SB and FDA regarding whether the original application (initial approval) would cover two indications (i.e. monotherapy and combination with metformin) or three indications (i.e. monotherapy, combination with metformin, and combination with SU). In an effort to expedite the review, as rosiglitazone NDA had been placed on a 6-month review clock, SB and FDA agreed that while all safety data for the SU studies would be incorporated into the initial approval, the efficacy data could be reviewed separately in an efficacy supplement post-approval. Nevertheless, all efficacy data files (as electronic data sets) were submitted to the initial NDA of November 24, 1998. Thus, all pivotal data for *Avandia* in combination with SU were submitted prior to the February 2, 1999 final rule date for financial disclosure.

SmithKline Beecham believes that the June 2, 1999 SU efficacy supplement is technically a re-submission of efficacy and safety data which has been previously reviewed and/or provided to FDA prior to February 2, 1999. For S-001, in fact, all safety data are provided by cross-reference only. For this reason, it is believed that financial disclosure information would not required for this supplemental application. We trust the Agency is in agreement.

Should you have any questions regarding this submission, please do not hesitate to contact me by phone at (610) 917-5907 or by fax at (610) 917-7665.

Sincerely,

Sharon W. Shapowal

Sharon W. Shapowal, R.Ph.
Director
U.S. Regulatory Affairs

Desk copy: Ms. Jena Weber (HFD-510)

APPEARS THIS WAY
ON ORIGINAL

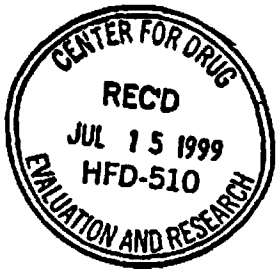
NDA SUPP AMEND
SE1-001-BS

DUPLICATE

July 8, 1999

Amendment to NDA 21-071/S-001
Avandia® (rosiglitazone maleate) Tablets

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine
Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857



Amendment to a pending sNDA:
FDA request for information - Biometrics

Dear Dr. Sobel:

Reference is made to our supplemental New Drug Application dated June 2, 1999, which was received by the Agency on June 3, 1999 and given the designation of S-001 to NDA 21-071. This efficacy supplement, containing clinical data, provides for the use of Avandia® (rosiglitazone maleate) Tablets in combination with sulfonylurea for the treatment of patients with Type 2 diabetes mellitus.

Further reference is made to communications between Ms. Joy Mele, of the Division of Biometrics II, and Dr. Michael Brennan of SmithKline Beecham. In a note received on May 26, 1999 from the Agency with regard to the data sets submitted in electronic format, Ms. Mele requested the following:

- A printout of 'Proc Contents' followed by a printout for about 50 observations for all analysis datasets, organized by study;
- A table of contents listing all the datasets submitted, organized by study;
- A SAS code for reading the datasets; and
- A data dictionary

REVIEWS COMPLETED
ACTION:
☐ N.A.I. ☐ MEMO
DATE

At this time, we are providing the following for each pivotal study (i.e. Protocols '015', '079', and '096')

- Table of Contents of Datasets
- SAS Code and Data Dictionary
- Proc Contents, and
- Proc Print of 50 observations.

While the actual SAS datasets in SAS transport file format have already been delivered as part of the submission to CDER, a separate set on CD could be supplied to reviewer Mele, if she prefers. We appreciate Ms. Mele's agreement to archiving of the large laboratory and vital signs files to the FDA server.

Should you have any questions regarding this supplemental New Drug Application, please do not hesitate to contact me by phone at (610) 917-5907 or by fax at (610) 917-7665.

Sincerely,

/S/

For
Sharon W. Shapowal, R.Ph.
Director
U.S. Regulatory Affairs

Desk copy: J. Weber (cover letter)

APPEARS THIS WAY
ON ORIGINAL

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NDA NO. 21-071 REF NO. 001
NDA SUPPL FOR SE1

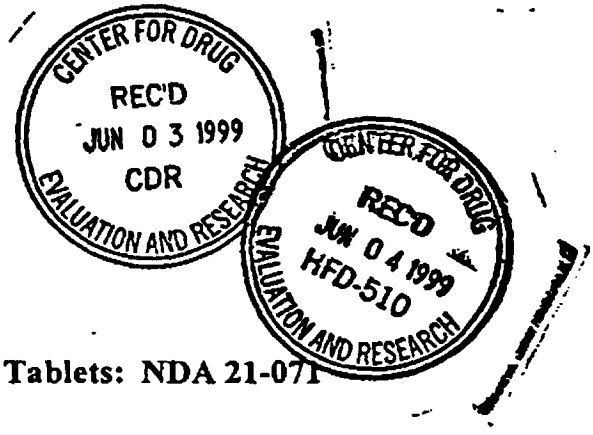
SmithKline Beecham
Pharmaceuticals June 2, 1999

DUPLICATE

NDA 21-071/S-001
Avandia® (rosiglitazone maleate) Tablets

Volumes 3.1.001, 3.8.001 – 3.8.045

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852



Avandia® (rosiglitazone maleate) Tablets: NDA 21-071

Dear Dr. Sobel:

Submitted herewith, in duplicate, in accordance with Section 314.50 of Title 21 of the Code of Federal Regulations is a supplemental New Drug Application to support the use of **Avandia® (rosiglitazone maleate) Tablets in combination with sulfonylurea for the treatment of patients with Type 2 diabetes mellitus.** *Avandia* is a thiazolidinedione, a new class of drugs, which activate PPARγ receptors and directly target insulin resistance, a fundamental defect in the pathophysiology of type 2 diabetes. The initial NDA 21-071 for *Avandia* as monotherapy and in combination with metformin was submitted on November 25, 1998 and was approved by FDA on May 25, 1999.

This supplemental New Drug Application (sNDA) specifically details the efficacy of *Avandia* in combination with sulfonylurea. Please note that in accordance with the request of the Division at the pre-NDA meeting held on April 30, 1998, the clinical safety data for this indication was included in the initial NDA with a clinical cut-off date of June 18, 1998. These safety data were updated on March 24, 1999 in the NDA Safety Update with a clinical cut-off date of November 6, 1998. As these safety data have already been reviewed and incorporated into the original NDA approval and labeling, they are not re-summarized herein, but are available in electronic data sets (see below).

Please be advised that the upper dose of *Avandia* was 4 mg per day in the pivotal controlled trials of this application. Data are not currently available on the use of *Avandia* 8 mg per day in combination with sulfonylurea.

One Franklin Plaza, PO Box 7929, Philadelphia, PA 19101. Telephone (215) 751 4000. Fax (215) 751 3400.

[

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Results of the Phase 3 studies provide evidence that 4mg/day rosiglitazone does not significantly potentiate sulfonylurea induced hypoglycemia. The monotherapy and combination metformin studies have previously demonstrated safety with doses of 4mg/day and 8mg/day of *Avandia*.

[

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As discussed on March 3, 1999 in a telephone conversation between Enid Galliers of FDA and Clare Kahn of SB, we are incorporating extensive sections of NDA 21-071 by cross-reference only. These sections are indicated in the Item 1 sNDA Index and also parenthetically in text where appropriate. The entire sNDA is being made available in electronic format to fully support the reviewers. Sections which are included by cross-reference to the initial NDA have been previously loaded onto the FDA network and remain available electronically to reviewers. The archival copy of this efficacy supplement consists of the paper sNDA (46 volumes) accompanied by Item 11 Case Report Form Tabulations in electronic format only as SAS transport files, in accordance with the most recent guidelines (January 1999).

Please note that the Agency had the efficacy and safety data sets of this application as part of the data sets provided with the original application. However, SB is re-submitting the SAS data sets now in accordance with the Guidance for Industry entitled, 'Providing Regulatory Submissions in Electronic Format', January 1999. A description of the electronic submission (contents of media, number/format, file descriptions, size of submission) are contained in the "Guide to the Electronic Submission" that appears in Volume 3.1.001.

The proposed draft labeling, herein submitted, has been highlighted by colored, underlined text to indicate where additions/changes are being proposed to the currently approved labeling for *Avandia*. This draft label is based upon the agreed

label in Word document format as of May 25, 1999. SmithKline Beecham technical editing is still preparing the final printed label for *Avandia*, which should be available shortly.

In accordance with the Prescription Drug User Fee Act of 1997, a check in the amount of [redacted] has been sent via wire transmittal to the FDA on May 24, 1999 (User Fee ID # 3725). A copy of the wire transfer receipt showing the submitted User Fee can be found in Item 18 of this volume.

Financial disclosure information has not been provided for investigators who participated in clinical trials of *Avandia* in combination with sulfonylurea. All principal studies demonstrating efficacy and safety for this indication were completed prior to the end of 1998.

Avandia was approved for the treatment of Type 2 diabetes mellitus in the United States on May 25, 1999 as monotherapy and in combination with metformin. It was also approved in Mexico on April 19, 1999 for these indications and in combination with sulfonylureas. [redacted]

[redacted] *Avandia* has not been refused marketing authorization or withdrawn from marketing in any country on safety grounds.

SmithKline Beecham commits to providing all necessary support for the review of this supplemental NDA including full technical support in the use of the electronic documentation.

Should you have any questions regarding this supplemental New Drug Application, please do not hesitate to contact me by phone at (610) 917-5907 or by fax at (610) 917-7665.

Sincerely,

Sharon W. Shapowal

Sharon W. Shapowal, R.Ph.
Associate Director
U.S. Regulatory Affairs