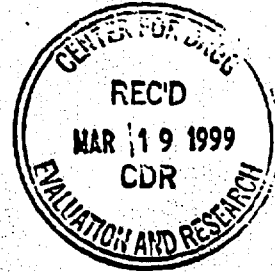


SB
SmithKline Beecham
Pharmaceuticals

March 18, 1999

NDA 21-071
Avandia™ (rosiglitazone maleate) Tablets
pp: 000001 - 000015

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



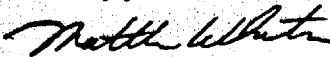
Response to FDA Request for Information

Dear Dr. Sobel:

Reference is made to our New Drug Application for Avandia™ (rosiglitazone) Tablets, NDA 21-071, indicated for the treatment of Type 2 diabetes mellitus as monotherapy and in combination with metformin. Additional reference is made to a February 23, 1999 fax from Ms. Jena Weber with questions from the Biopharmaceutics reviewer. In response, we faxed a reply directly to Dr. Michael Fossler on March 2, 1999 and sent a supporting diskette to him directly on the same day.

With this letter, we are providing a copy of this fax and the supporting diskette for FDA's archives. Please contact me at (610) 917-7250 via phone or (610) 917-7665 via facsimile should you have any questions regarding this submission.

Sincerely yours,


for Clare Kahn, Ph.D.
Group Director
U.S. Regulatory Affairs

Cover Letter: Ms. Jena Weber, HFD-510

000001

ORIGINAL
SB

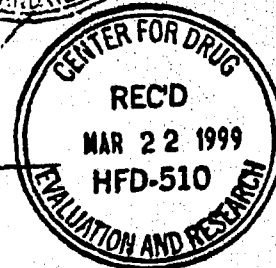
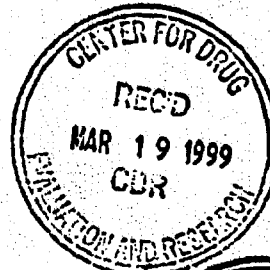
SmithKline Beecham
Pharmaceuticals

ORIG AMENDMENT
BP

March 18, 1999

NDA 21-071
Avandia™ (rosiglitazone maleate) Tablets
pp: 000001 - 000037

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



Response to FDA Request for Information

Dear Dr. Sobel:

Reference is made to our New Drug Application for Avandia™ (rosiglitazone) Tablets, NDA 21-071, indicated for the treatment of Type 2 diabetes mellitus as monotherapy and in combination with metformin. Additional reference is made to a February 11, 1999 meeting with Dr. Herman Rhee for electronic NDA training. In response to questions he raised at this meeting, we faxed him two sets of responses on February 24, 1999. An additional fax was sent to Dr. Rhee on March 15, 1999.

With this letter, we are providing a copy of these faxes for FDA's archives. Please contact me at (610) 917-7250 via phone or (610) 917-7665 via facsimile should you have any questions regarding this submission.

Sincerely yours,

Clare Kahn
for Clare Kahn, Ph.D.
Group Director
U.S. Regulatory Affairs

Cover Letter: Ms. Jena Weber; HFD-510

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO

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Pharmaceuticals

NEW CORRESP

March 4, 1999

NDA 21-071
Avandia™ (rosiglitazone maleate) Tablets

Daniel Boring, Ph.D. (HFD-530)
Secretary, Nomenclature Standards Committee
Room S-447
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



Request for Expedited Review of the AVANDIA trademark by the Nomenclature Standards Committee

Dear Dr. Boring:

Reference is made to our NDA 21-071 for Avandia™ (rosiglitazone maleate) Tablets submitted to FDA on November 25, 1998. This NDA is currently under review in the Metabolism and Endocrine Division and has been granted a six-month priority review designation.

In light of these accelerated timings, it is imperative to SB Pharmaceuticals that the AVANDIA trademark be reviewed by the FDA Nomenclature Committee as quickly as possible. Therefore, we are urgently requesting the Nomenclature Committee to review the AVANDIA trademark at its next scheduled meeting, which we understand is held on the fourth Tuesday of the month (March 23rd). Following the meeting, we would greatly appreciate receiving any comments from the Committee at the earliest opportunity.

Thank you for your consideration of this matter. Should you have any questions regarding this request, please contact me by phone at (610) 917-7250 or by fax at (610) 917-7665.

Sincerely,

G. Clare Kahn, Ph.D.
Group Director, U.S. Regulatory Affairs

Desk copies: Ms. Jena Weber, HFD-510
Dr. Xavier Ysem, HFD-510

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

SB
SmithKline Beecham
Pharmaceuticals
FACSIMILE

March 4, 1999

To: Daniel Boring, Ph.D.
Executive Secretary
Nomenclature Standards Committee Fax No.: (301) 827-2520
Phone No.: (301) 827-2396

From: Clare Kahn, Ph.D./SmithKline Beecham Fax No.: (610) 917-7665
Phone No.: (610) 917-7250

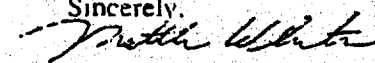
Regarding: NDA 21-071 – Request for Expedited AVANDIA Trademark Review

Page 1 of 2

Dear Dr. Boring:

With the attached letter, we are requesting review of the AVANDIA trademark at the next Nomenclature Committee meeting which we understand is held on the fourth Tuesday of the month (March 23, 1999). The NDA for AVANDIA (rosiglitazone maleate) Tablets was submitted November 25, 1998 and has been granted a six-month priority review by the Metabolism & Endocrine Drugs Division. Thank you for your assistance in this matter.

Please give me a call if you wish to discuss any of this further.

Sincerely,

for Clare Kahn, Ph.D.

Copy: Ms. Jena Weber (IIFD-510)
Dr. Xavier Ysem (HFD-510)

SB
SmithKline Beecham
Pharmaceuticals

March 3, 1999

NDA 21-071
Avandia™ (rosiglitazone maleate) Tablets

Moh Jee Ng, Ph.D.
Division of Biometrics II - Room 10 B06
(HFD-715)
Document Room 14-B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Jena
DR sent
to ANg on 3/8/99



Response to FDA Request for Information

Dear Dr. Ng:

Reference is made to our New Drug Application for Avandia™ (rosiglitazone) Tablets, NDA 21-071, indicated for the treatment of Type 2 diabetes mellitus as monotherapy and in combination with metformin. Additional reference is made to our February 4, 1999 submission of datasets for animal carcinogenicity studies. On February 24, 1999, Ms. Jena Weber relayed a request to us for an additional printed copy of this submission which was sent to you on February 25, 1999.

On March 2, 1999, you spoke with Matthew Whitman and clarified that you would like a copy of the animal carcinogenicity study reports (NDA Volumes 1.5.034-1.5.041). Attached with this letter are the requested volumes.

If you have any questions or requests regarding these data, please do not hesitate to contact me at (610) 917-7250 or my associate, Matthew Whitman, at (610) 917-5302.

Sincerely,

A handwritten signature in cursive script that reads 'Clare Kahn'.

Clare Kahn, Ph.D.
Group Director
U.S. Regulatory Affairs

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



SmithKline Beecham
Pharmaceuticals

February 25, 1999

NDA 21-071
Avandia™ (rosiglitazone maleate) Tablets

Moh Jee Ng, Ph.D.
Division of Biometrics II (HFD-715)
Document Room 14-B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Response to FDA Request for Information

Dear Dr. Ng:

Reference is made to our New Drug Application for Avandia™ (rosiglitazone) Tablets, NDA 21-071, indicated for the treatment of Type 2 diabetes mellitus as monotherapy and in combination with metformin. Additional reference is made to our February 4, 1999 submission of datasets for animal carcinogenicity studies.

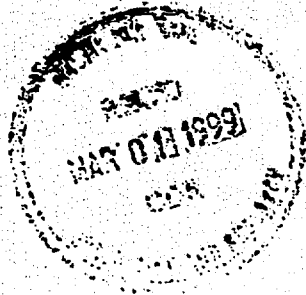
On February 24, 1999, Ms. Jena Weber relayed a request to us for an additional printed copy of this submission. Attached with this letter is a printed copy of the animal carcinogenicity datasets.

If you have any questions or requests regarding these data, please do not hesitate to contact me at (610) 917-7250 or my associate, Matthew Whitman, at (610) 917-5302.

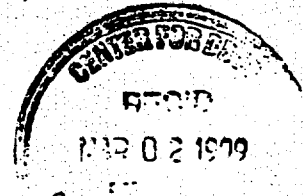
Sincerely,

for
Clare Kahn, Ph.D.
Group Director
U.S. Regulatory Affairs

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



February 22, 1999



NDA 21-071
Avandia™ (rosiglitazone maleate) Tablets

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

**Response to FDA Request: Submission of Population Pharmacokinetic
Data Files**

Dear Dr. Sobel:

Reference is made to our NDA 21-071 for Avandia™ (rosiglitazone maleate) Tablets dated November 24, 1998. Additional reference is made to a telephone conversation on February 11, 1999 between Dr. Michael Fossler of FDA and Dr. Bela Patel of SB to discuss the review of Avandia population pharmacokinetic analysis.

Dr. Fossler inquired about Appendix F of the population pharmacokinetic report (SB Report No. BRL-049653/RSD-100T7L/1, "Population pharmacokinetic analysis of rosiglitazone in patients with Type 2 diabetes mellitus", located in NDA Item 6J: Volume 1.6.030) which displayed a hard copy of the NONMEM output files. These output files had been truncated in the report and did not include some of the information he wanted. Therefore, we are providing a complete copy of the data, control streams and outputs on the enclosed compact disc. An outline of the material being provided within the three folders on the disc follows:

Submission of Control Streams, Datasets and Outputs

1) Control Streams: A total of 98 individual control streams that were tested in NONMEM including:

- a) Basic model (model # 63)
- b) Final model (model # 89) The final model was tested multiple times using different initial parameter estimates (model #'s 89A, 89B, 89C)
- c) Impact of outliers on the basic model (model # 92)
- d) Impact of outliers on the final model (model # 93)
- e) Evaluation of the final model using the validation data set (model # 94)
- f) Bayesian predictions for the validation data set using the final model priors (model # 95)

2) Datasets:

- a) p3spt25b.csv used for the entire model building process as well the objective function mapping
- b) p3fullspt28b.csv used to examine the influence of outliers on the basic and final model
- c) valspt28.csv used for the estimation of the parameters as well as the Bayesian predictions for the validation data set using the final model priors

3) NONMEM Outputs:

A total of 9 outputs have been provided which include the following:

- a) NONMEM output for the basic model (model # 63)
- b) NONMEM outputs for the final model (model #'s 89, 89A, 89B and 89C)
- c) NONMEM output for the impact of outliers on the basic model (model # 92)

3) NONMEM Outputs (cont'd):

d) NONMEM output for the impact of outliers on the final model
(model # 93)

e) NONMEM output for the estimation of population parameters using the
final model for the validation data set (model # 94)

f) NONMEM output for the individual and population Bayesian predictions
for the validation data set (model # 95)

Should you have any questions regarding this New Drug Application, please do not
hesitate to contact me by phone at (610) 917-7250 or by fax at (610) 917-7665.

Sincerely,



G. Clare Kahn, Ph.D.
Group Director
U.S. Regulatory Affairs

Cover Letter & CD: Dr. Michael Fossler, HFD-510

Cover Letter: Ms. Jena Weber, HFD-510

SB
SmithKline Beecham
Pharmaceuticals



February 18, 1999

NDA 21-071
Avandia™ (rosiglitazone maleate) Tablets
pp: 000001 - 000382

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

Response to FDA Request for Information

Dear Dr. Sobel:

Reference is made to our New Drug Application for Avandia™ (rosiglitazone) Tablets, NDA 21-071, indicated for the treatment of Type 2 diabetes mellitus as monotherapy and in combination with metformin. Additional reference is made to a fax from Ms. Jena Weber on February 2, 1999 requesting additional dissolution and method validation data to assist in the review of this Application.

With this letter, we are providing our response to the four queries received via fax. For your convenience, FDA questions are provided in bold type, followed by SB's response. Supporting reports are also attached with this letter. A Table of Contents for this submission is located on page 000006.

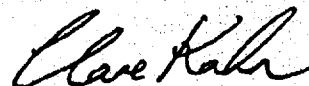
We are also taking the opportunity to provide two replacement figures for NDA Item 6B.7 (pages 000381 and 000382 of this submission which replace pages 000038 and 000040 of NDA Volume 1.6.001, respectively). These figures were incorrectly placed into the original NDA document.

000001

NDA 21-071
February 18, 1999
Page 2

Please contact me at (610) 917-7250 via phone or (610) 917-7665 via facsimile should you have any questions regarding this submission.

Sincerely yours,



Clare Kahn, Ph.D.
Group Director
U.S. Regulatory Affairs

Desk Copy: Rob Shore, Pharm.D.; HFD-870 (Sent separately)

Cover Letter: Ms. Jena Weber; HFD-510

000002

SB
SmithKline Beecham
Pharmaceuticals

BM

OTG AMERICA
Ciba

January 28, 1999

NDA 21-071
Avandia™ (rosiglitazone maleate) Tablets
Volumes 1 - 11

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

Response to FDA Request for Information

Dear Dr. Sobel:

Reference is made to our New Drug Application for Avandia™ (rosiglitazone) Tablets, NDA 21-071, indicated for the treatment of Type 2 diabetes mellitus as monotherapy and in combination with metformin. Additional reference is made to communications on December 17, 1998 and January 4, 5, and 8, 1999 with Dr. Hsien Ju of the Clinical Investigations Branch (HFD-344) in which he requested and we provided investigator and patient information from our pivotal studies (011, 024, 093, 094) supporting this NDA.

In response to Dr. Ju's January 8th request, we are now providing additional information for the following investigator study sites:

- Study 011: Dr. Andrew Lewin (Center 007) – Los Angeles, CA
- Study 024: Dr. Jeffrey Herbst (Center 052) – Portland, OR
- Study 093: Dr. James Snyder (Center 033) – Las Vegas, NV
- Study 094: Dr. Jack Wahlen (Center 007) – Ogden, UT

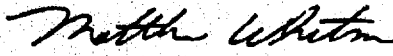
Attached for each study center is a 1572 form, copy of the protocol and amendments, total number of patients randomized and completed, a list of dropouts and reason(s) for withdrawal, a list of adverse events for all patients, a copy of all signed informed consent documents, and the identified case report forms. A Table of Contents for this submission is attached following this letter.

NDA 21-071
January 28, 1999

2

Please contact me at (610) 917-7250 via phone or (610) 917-7665 via facsimile should you have any questions regarding this submission.

Sincerely yours,



for Clare Kahn, Ph.D.
Group Director
U.S. Regulatory Affairs

Desk Copy: Hsien Ju, M.D.; HFD-344 (Sent under separate cover)

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
INITIALS	DATE

1572 Form

Protocol

Patents/Trademarks/US
Completed

Patent Withdrawal/US
Reason

Adverse Events

SB
SmithKline Beecham
Pharmaceuticals

January 11, 1999



NDA 21-071
Avandia™ (rosiglitazone maleate) Tablets

Volume 2.3.001

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

Minor Corrections - Item 3/Replacement Volume

Dear Dr. Sobel:

Reference is made to our NDA 21-071 for Avandia™ (rosiglitazone maleate) Tablets submitted on November 25, 1998. Additional reference is made to a telephone conversation with the project manager, Ms. Jena Weber, on January 5, 1999 to discuss submission of minor corrections/clarifications to Item 3 of this NDA.

As we mentioned to Ms. Weber, in preparing the electronic submission for this file, minor inconsistencies, which do not affect content or interpretation of data, were noted between the paper copy and the electronic submission. In order to maintain consistency between the paper and electronic files, we are providing a replacement paper Item 3 volume, with the following changes.

Item 3A - Annotated Labeling: For the Canadian New Drug Submission, a deeper level of annotation was required. We are providing this to assist you in your review.

Item 3E - Preclinical Summary: Information on metabolism in the female rat was added.

Item 3F - Human Pharmacokinetics: Reference List corrected. In-text references were incorrect by one number in the previous list.

NDA 21-071
January 11, 1999
Page 2

rather than provide individual replacement pages for the revisions to this volume, we thought it would be easier to provide a new Item 3 volume (attached).

Should you have any questions regarding this New Drug Application, please do not hesitate to contact me by phone at (610) 917-7250 or by fax at (610) 917-4708.

Sincerely,

Matthew Wilkerson
for G. Clare Kahn, Ph.D.
Group Director
U.S. Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL



SmithKline Beecham
Pharmaceuticals

Regulatory Affairs - U.S.
Anti-Infectives and Biological Therapeutic Areas

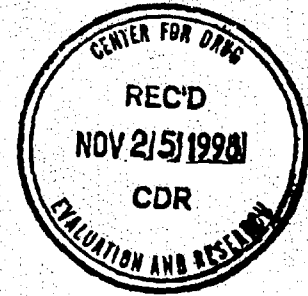
NDA 21-071

Avandia™ (rosiglitazone maleate) Tablets

November 24, 1998

Volumes 1.1001 - 1.8.172

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 New Drug Application to support the use of *Avandia*™ (rosiglitazone maleate) Tablets for the treatment of patients with Type 2 diabetes mellitus. *Avandia*™ is a thiazolidinedione, a new class of drugs, which activates PPAR γ receptors and directly targets insulin resistance, a fundamental defect in the pathophysiology of type 2 diabetes.

SB acknowledges the guidance received from the Division of Metabolic and Endocrine Drug Products at the End of Phase II Meeting held on July 22, 1996 and the Pre-NDA Meeting held on April 30, 1998. Please note, specifically that, in accordance with the request of the Division at the pre-NDA meeting, although the efficacy data herein support two indications, the safety data for all patients receiving Avandia for any indication are included in the safety evaluation with a clinical cut-off date of June 18, 1998.

This Application details the efficacy, safety, and clinical pharmacology data for the intended use of rosiglitazone - two indications in the treatment of hyperglycemia of type 2 diabetes mellitus as follows:

- as monotherapy and
- in combination with metformin (coadministration)

Avandia™ (rosiglitazone maleate)

NDA Cover Letter

November 24, 1998

Over 4300 patients and 500 volunteers have received the drug in protocols of single or repeated dosing for periods up to 18 months. The integrated safety database is substantial, both in terms of patient numbers and by duration of exposure, with 4327 patients exposed to rosiglitazone (as monotherapy or in combination with metformin or sulfonylureas); more than 2600 patients were exposed for at least 6 months and 1005 patients exposed for at least 12 months. In addition, 222 patients were exposed to rosiglitazone in long-term echocardiography studies.

The entire NDA is made available in electronic copy to fully support the reviewers. The archival copy consists of the paper NDA (261 volumes) accompanied by the following items in electronic format only in accordance with the existing (September, 1997) Guidance for Electronic Submissions:

- Item 11 Case Report Form Tabulations and
- Item 12 Case Report Forms.

The entire electronic submission will be loaded on the FDA network. Arrangements will be made to have this file loaded as soon as possible. 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 prefaces the NDA Index.

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 November 20, 1998 [REDACTED]. A copy of the wire transfer receipt showing the submitted User Fee is in Item 18 of this volume.

Avandia™ is not approved for the treatment of Type 2 diabetes mellitus in any country; the first marketing applications for the use of *Avandia™* in this indication will be submitted in November/December 1998 in the United States, Canada and in Europe. *Avandia™* has not been refused marketing authorization or withdrawn from marketing in any country on safety grounds.

In consideration of our clinical trial results, SB Pharmaceuticals believes *Avandia™* to be an important treatment option for patients with type 2 diabetes mellitus that warrants a Priority Review. The potential basis for Priority Review

Avandia™ (rosiglitazone maleate)

NDA Cover Letter

November 24, 1998

has been discussed and agreed with the Division at the Pre-NDA meeting and during informal contacts thereafter. As a result of these discussions, we respectfully request Priority Review status on the following basis:

- **Liver safety**

Only one thiazolidinedione has been approved for use in the management of patients with Type 2 diabetes to date. There is a clear need for another member of this class which is not associated with significant safety issues including hepatotoxicity. To date, the safety data from approximately 4300 patients treated with rosiglitazone, 1000 of whom were exposed for greater than 12 months, have not been associated with hepatotoxicity or any other major adverse effects. We believe that this feature would present the primary basis for a Priority Review.

- **Novel Indication:**

The indication of combined use of *Avandia™* with metformin constitutes a novel indication in Type 2 diabetes mellitus

In addition, the potential for common drug interactions with *Avandia™* appears to be low.

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

Should you have any questions regarding this New Drug Application, please do not hesitate to contact me at (610) 917-7250.

Sincerely,



G. Clare Kahn, Ph.D.
Group Director
U.S. Regulatory Affairs