

SB
SmithKline Beecham
Pharmaceuticals

000001

May 7, 1999

Avandia® (rosiglitazone maleate)
NDA 21-071
Amendment to a Pending NDA

DESK COPY
Cover Letter
Mrs. Jena Weber

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

**Amendment to a Pending NDA – Response to FDA Request for Information
and Updated Information**

Dear Dr. Sobel:

Reference is made to the New Drug Application for *Avandia*, NDA 21-071. The NDA provides for use of a novel PPAR γ receptor activator for the treatment of hyperglycemia in type 2 diabetes mellitus, as monotherapy and in combination with metformin.

In a May 3, 1999 telephone conversation between Dr. Robert Shore (FDA) and Mr. Matt Whitman and Ms. Dale Stockbower (SB), it was requested that additional dissolution profile data be generated, to compare the 2 mg and the 4 mg commercial tablets in accordance with the requirements of a SUPAC-IR Level 2 composition change. It was agreed that data for the application media

[REDACTED]

[REDACTED]

NDA 21-071
 Avandia® (rosiglitazone maleate) Tablets

Submitted herein, is the requested dissolution information [REDACTED]

Additionally, in an April 19, 1999 telephone conversation between Dr. Xavier Ysem (FDA) and Ms. Dale Stockbower (SB) it was agreed that the results of the drug product validation studies could be used [REDACTED]

Provided below are the currently filed [REDACTED] and the [REDACTED] to be applied to commercial manufacture. We commit that the commercial Avandia® tablets will meet the filed drug product specifications, and that no changes are proposed to these specifications. Updated batch records will be submitted in the annual report.

Tablet Strength	Parameter	Current NDA	Commercial Manufacture
1, 2, 4 mg	[REDACTED]	[REDACTED]	[REDACTED]
8 mg	[REDACTED]	[REDACTED]	[REDACTED]

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

APPEARS THIS WAY ON ORIGINAL [REDACTED]

Sincerely yours,

Clare Kahn

Clare Kahn, Ph.D.

Group Director

U.S. Regulatory Affairs

Desk Copy: Dr. Robert Shore, HFD-870

Desk Copy: Dr. Xavier Ysem, HFD-510

Cover Letter: Ms. Jena Weber, HFD-510

SB
SmithKline Beecham
Pharmaceuticals
FACSIMILE

May 5, 1999

To: Jena Weber (HFD-510)

Fax No.: (301) 443-9282

From: Clare Kahn, Ph.D./SmithKline Beecham

Fax No.: (610) 917-7665

Phone No.: (610) 917-7250

Regarding: NDA 21-071 – Request for Revised Annotated Labeling and
Outline of Phase IV Commitments

Page 1 of 40

Dear Jena,

Attached is revised annotated labeling incorporating those changes made as a result of FDA's medical and statistical reviews and the recommendations of the Metabolism and Endocrine Advisory Committee.

Also provided is the proposed phase IV post-marketing plan. For the past several months, SB has been debating the design of longer term outcomes trials with the new thiazolidenedione, rosiglitazone, and has been in discussions with external advisors to this end. Preventing disease progression is an area that would be most interesting to investigate. Such trials could also address additional areas of interest. However, given the scope, complexity, and expense of such trials, SB is not currently in a position to make any commitment about a long term outcomes trial. We are, however, able to offer the current post-marketing plan (Phase IV) which is attached. We look forward to agreement with the FDA team.

Copies of these documents will also be submitted officially to the NDA file.

Sincerely,

Clare Kahn

Clare Kahn, Ph.D.

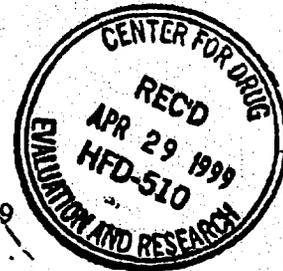


ORIG AMENDMENT
52

DUPLICATE

SmithKline Beecham
Pharmaceuticals

Avandia® (rosiglitazone maleate)
NDA 21-071
Amendment to a Pending NDA



April 28, 1999

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

**Amendment to a Pending NDA: Corrections to immediate container/carton labels
Submission of draft cartons for Patient Trial Kit**

Dear Dr. Sobel:

Reference is made to the New Drug Application for *Avandia*, NDA 21-071. The NDA provides for use of a novel PPAR γ receptor activator for the treatment of hyperglycemia in type 2 diabetes mellitus, as monotherapy and in combination with metformin. Reference is further made to the most recent, April 12, 1999, submission of draft mechanical labeling for the immediate containers and blister sample cartons.

As communicated in a telephone conference call the morning of April 21, 1999, involving Dr. Ysern from the division and Ms. Shapowal and Mr. Kitz from SmithKline Beecham, an error has been caught on the sample cartons that were submitted on April 12, 1999. The text, "Protect from light" was placed after the previously agreed temperature storage statement. The text was placed on the 2 mg, 4 mg, and 8 mg sample cartons. There is no data in the NDA to suggest that such a statement is required to maintain the stability of the product. We apologize for not catching this text before submission.

As noted by Mr. Kitz, a 'protect from light' notation might cause undue concern for the customers, and at the next printing of the sample cartons, SB wishes to remove the language. Unfortunately, a substantial number of the cartons for the blisters have been printed for the launch of *Avandia*. Given the cost of the printed components, the long lead time for having such cartons reprinted, and the imminence of the launch of *Avandia*, *SmithKline Beecham respectfully requests permission to use the sample cartons for the initial launch and to delete the text "Protect from light" at the next printing.* SmithKline Beecham commits to submitting the corrected, final sample cartons in the first annual report.

Letter to Dr. Sobel
April 28, 1999

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Further, any of the bottles that might be repackaged by customers (i.e. bottle counts of 100, 500 or 5000 tablets) should carry the standard USP statement "Dispense in a tight, light-resistant container". Any of the manufacturer's bottles designed and intended to be dispensed to patients without repackaging (i.e. bottle counts of 30 and 60 tablets) should not carry any statement regarding type of container to be used in dispensing [ref. 21 CFR 201.100(b)(7)]. The immediate container labels will be revised, accordingly. These labels have not been printed by the sponsor. However, final printed labels will be submitted as part of the final labeling approval process.

Finally, please find enclosed outer carton labels that are identified by "Patient Trial Kit". These cartons will contain patient samples of 2 mg or 4 mg bottles of 60 or 30 tablets, respectively. These cartons correspond to the immediate container bottle labels filed on April 12, 1999.

Thank you for your kind attention to the labeling matters of this amendment. We apologize for any confusion regarding the 'Protect from light' text, and thank Dr. Ysem for speaking with our team at such short notice. Please let us know that you are in agreement with our corrective action plan and intended use of the printed components for launch only. Should you have any questions regarding this issue, please do not hesitate to contact me at (610) 917-7250.

Sincerely,



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

cc: J. Weber (HFD-510)
X. Ysem (HFD-510)
P. Kitz (FP-0630)

APPEARS THIS WAY ON ORIGINAL

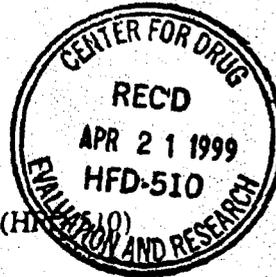
SB
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NDA AMENDMENT
April 20, 1999

Avandia® (rosiglitazone maleate)
NDA 21-071
Amendment to a Pending NDA

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



Amendment to a Pending NDA - Response to FDA Request for Information

Dear Dr. Sobel:

Reference is made to the New Drug Application for Avandia, NDA 21-071. The NDA provides for use of a novel PPAR γ receptor activator for the treatment of hyperglycemia in type 2 diabetes mellitus, as monotherapy and in combination with metformin.

In a fax dated April 16, 1999, Dr. Misbin requested additional patient details about the hematological history on the following patients:

4 patients with anemia as SAE: 004.70042, 024.030.02226, 020.720.01004 and any additional patients with myelodysplastic syndrome. (Narratives for these 4 patients were faxed to Dr. Misbin's attention on April 20, 1999.)

9 patients in table 8H.8.13 identified with low F3 hematocrit

9 patients in table 8H.8.17 with low F3 wbc and 5 patients with low F3 platelets

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> NAI <input type="checkbox"/> MEMO
DATE

NDA 21-071
Avandia® (rosiglitazone maleate) Tablets

Attached are narratives for those patients who demonstrated transitions in hematology tests from Normal or F1 at Baseline to F3 flags.

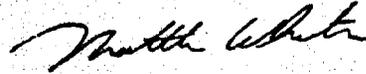
Normal to F3 flag: Lab values were normal at baseline transitioning to F3 flag on-therapy or within 30 days post-therapy.

F1 to F3 flag: Lab values were abnormal (F1 flags) at pre-randomization/baseline.

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

APPEARS THIS WAY ON ORIGINAL

Sincerely yours,



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

Desk Copy: Dr. Robert Misbin, HFD-510

Cover Letter: Ms. Jena Weber; HFD-510

APPEARS THIS WAY ON ORIGINAL

SB
SmithKline Beecham
Pharmaceuticals

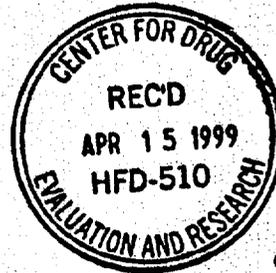
RB

ORIG AMENDMENT

April 13, 1999

NDA 21-071
Avandia® (rosiglitazone maleate) Tablets
pp: 000001 - 000032

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 April 9, 1999 telephone call from Dr. Rob Shore requesting the SAS command files and the ASCII datasets on diskette for study 49653/028, titled, *Bioequivalence Study of the Final Market Formulation of BRL 49653C Compared to the Clinical Trials Formulation*.

Attached with this letter are a copy of these files on diskette and as a paper copy for FDA's archives. A desk copy of this submission is also enclosed for Dr. Shore. 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

SI
4/26/99

Desk copy: Dr. Rob Shore, HFD-870
Cover Letter: Ms. Jena Weber, HFD-510

REVISIONS

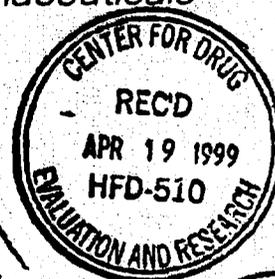
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		<input type="checkbox"/> MEMO
		DATE

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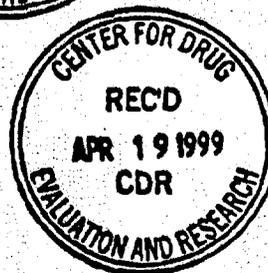
NEW CORRESP



April 13, 1999

NDA 21-071
Avandia® (rosiglitazone maleate) Tablets

Solomon Sobel, M.D.
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852



Response to FDA Request for Information

Request for Deferral of Pediatrics Studies Until After NDA Approval

Dear Dr. Sobel:

Reference is made to our NDA 21-071 for Avandia® (rosiglitazone maleate) Tablets submitted to FDA on November 25, 1998 for the treatment of Type 2 diabetes mellitus as monotherapy and in combination with metformin. Additional reference is made to your letter dated March 30, 1999 stating Avandia has been granted a six-month priority review and outlining the new pediatric labeling requirements of 21 CFR 314.55, which became effective April 1, 1999.

We note the final rule permits the submission of pediatric study information to be deferred until after approval if there is an adequate justification for deferral, e.g., because pediatric studies should not begin until after safety and efficacy information in adults has been collected, or awaiting completion of pediatric studies would delay the availability of a product to adults. We believe that both of these examples apply to Avandia and with this letter, we are formally requesting a deferral of pediatric studies until after approval of NDA 21-071 for Avandia.

Type 2 diabetes is generally a disease of adults that increases in prevalence with advanced age. We recognize, however, that increasingly, coincident with an increasing prevalence of obesity in children and adolescents, a syndrome of insulin resistance and type 2 diabetes mellitus is being observed to be on the rise in these younger individuals.

As you are aware, Avandia was granted a priority review by the Division primarily based on an improved hepatic safety profile as compared with the only marketed thiazolidinedione,

NDA 21-071
Dr. Sobel letter
April 13, 1999

Rezulin™ (troglitazone). Troglitazone has been demonstrated to cause rare cases of liver failure in adults, the magnitude of which only became fully apparent with postmarketing experience. As outlined in the final pediatric rule, in certain cases, studies should not begin in pediatric patients until after the safety profile of the drug is well established through postmarketing experience. Although, there is no evidence for hepatotoxicity with *Avandia* in clinical trials in over 4600 treated patients, we believe that it is appropriate to delay the initiation of pediatric studies with *Avandia* until after it has been approved and marketed.

To ensure that deferral of studies would not unnecessarily delay the submission of pediatric use information, SB plans to submit an outline of planned pediatric studies to the Division, following the marketing approval of *Avandia*. We will be happy to discuss and agree these plans with members of the Division at that time.

If you have any questions regarding this submission, please do not hesitate to contact me by telephone at (610) 917-7250 or by fax at (610) 917-7665.

Sincerely,

Clare Kahn

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

OK
[Redacted]
4/27/99

APPEARS THIS WAY ON ORIGINAL

Desk Copy: Ms. Jena Weber

REVIEWS COMPLETED	
CSO ACTION:	
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CSO INITIALS	DATE

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SB
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Pharmaceuticals

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ORIG AMENDMENT
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April 12, 1999

NDA 21-071
Avandia® (rosiglitazone maleate) Tablets
pp. 000001 - 000027

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

Solomon Sobel, M.D.
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852



Submission of Avandia® Sample and Carton Labels

Dear Dr. Sobel:

Reference is made to our NDA 21-071 for Avandia® (rosiglitazone maleate) Tablets submitted to FDA on November 25, 1998 for the treatment of Type 2 diabetes mellitus as monotherapy and in combination with metformin. Additional reference is made to a telephone conversation between SB and Dr. Xavier Ysern on April 9, 1999 to discuss our April 1, 1999 submission of the proposed Avandia Logo and professional sample labels and cartons.

We understand Dr. Ysern's comments were unofficial since his chemistry review has not yet been signed off within the Division. However, based on his feedback we have made the following changes to our labels and sample cartons:

- 1) The uniform storage statement has been revised to include the specified wording of the June 1998 draft FDA Guidance, titled, "Stability Testing of Drug Substances and Drug Products", as follows:

Store at 25°C (77°F); excursions 15-30°C (59-86°F)
- 2) We have revised some of the colors used on the 2 mg, 4 mg, and 8 mg tablet boxes so these boxes are more readily distinguishable from each other at a glance.

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N21071

NDA 21-071

Dr. Sobel letter
April 12, 1999

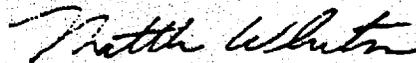
With respect to the use of the proprietary name, "Tiltab®" in labeling, it is SB policy to use this designation in our labeling. The following SB marketed products are cited as examples of its use.

- 1) *Tagamet*: 400mg and 800mg Tiltab® Tablets Referenced in PI and Labels.
- 2) *Coreg*: 6.25mg, 12.5mg and 25mg Tiltab® Tablets Referenced in PI and Labels.
- 3) *Requip*: 0.25mg, 5mg, 1mg, 2mg and 5mg Tiltab® Tablets Referenced in PI.

A Table of Contents for this submission is located on page 000008.

In order to maintain current timings for printing and production, we are seeking FDA comment on these materials as quickly as possible. We will contact the CSO, Ms. Jena Weber, later in the week for any comments on these materials. If you have any questions regarding this submission, please do not hesitate to contact me by telephone at (610) 917-7250 or by fax at (610) 917-7665.

Sincerely,



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

Desk copy: Dr. Xavier Ysern
Cover letter: Ms. Jena Weber

APPEARS THIS WAY ON ORIGINAL

000002

SB
SmithKline Beecham
Pharmaceuticals

ORIGINAL

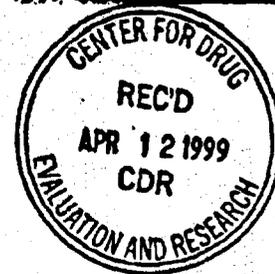
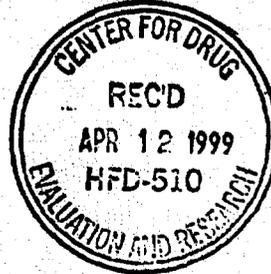
Avandia® (rosiglitazone maleate)
NDA 21-071
Amendment to a Pending NDA

ORIG AMENDMENT
ZML

April 7, 1999

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

Solomon Sobel, M.D.
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852



Amendment to a Pending NDA -
Response to FDA Request for Clarification

noted
[Redacted]
4/20/99

Dear Dr. Sobel:

Reference is made to the New Drug Application for *Avandia* (rosiglitazone maleate), NDA 21-071. The NDA provides for use of a novel PPAR γ receptor activator for the treatment of hyperglycemia in type 2 diabetes mellitus, as monotherapy and in combination with metformin.

At this time, we are responding to the request of medical officer, Dr. Robert Misbin, that the sponsor provide documentation to support that Protocol 49653/011 was conducted in a manner such that the rights and safety of human subjects were adequately protected. Dr. Misbin's primary concern focuses on the adequacy of written informed consent documentation advising patients with type 2 diabetes mellitus of the risks potentially associated with withdrawal of prior therapy and use of placebo controls together with diet and exercise in this 6 month study.

Dr. Misbin has noted in telephone conversations on March 24 and April 1, 1999, that, following review of the consent forms from our pivotal efficacy trials submitted to NDA 21-071, he is considering the censure of data from study 011. During the April 1st conversation, Dr. Misbin noted that he was willing to accept the data from previously drug-naïve patients as this subset of patients had not been withdrawn from active drug treatment. Reference was made to 21 CFR §314.125, Refusal to approve an application or abbreviated antibiotic application:

000001

"Any clinical investigation involving human subjects described in the application or abbreviated antibiotic application, subject to the institutional review board regulations in part [56] of this chapter or informed consent regulations in part 50 of this chapter, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected."

SmithKline Beecham is sensitive to the concerns of Dr. Misbin for patient safety and protection and wishes to address his concerns herein. Indeed, we had the opportunity recently, to address Dr. Misbin's concerns about the ceiling for hyperglycemia in our IND protocol 49653C/127 entitled "A 26 week Randomized, Double-blind Study to Compare the Efficacy, Safety and Tolerability of Rosiglitazone (BRL 49653C) 8mg/day (4mg BID) Versus Placebo in Combination with Glyburide in Patients with Type 2 Diabetes Mellitus Who Are Inadequately Controlled on Maximum Dose Glyburide". A meeting with the Division lead to the immediate resolution of this issue with the institution of tighter controls for glycemia which we have endorsed for all subsequent studies.

Protocol 49653/011 was initiated in 1996 under an Investigational New Drug application. There was strict adherence to all regulations and procedures governing the conduct of an ethical clinical trial. A sample consent form was provided by SB and seventeen independent IRBs, overseeing 43 sites, reviewed, modified and approved consent forms for the conduct of this study. Over a period of almost 3 years, no ethical concerns were ever raised regarding inadequacy of protection of the rights or safety of the patients taking part in the trial. Furthermore, no concerns were raised at the pre-NDA meeting on April 30, 1998, at which time it was agreed that Study 011 provided key pivotal data for our monotherapy indication. As a result of this agreement, all of the safety and efficacy data from study 011 were filed to this NDA. Furthermore, these data contributed to the Integrated Summary of Safety and several important efficacy analyses were performed on pooled data from pivotal and extension studies including study 011.

SmithKline Beecham believes that study 011 was conducted in an ethical manner. In this submission, we seek to confirm this view with a survey of consent forms approved by the 17 independent IRBs. We do acknowledge that a typographical error existed in the sample consent form in that patients were asked to bring all of their study medication "and glibenclamide" tablets to the clinic at each visit. This error appears to have been picked up at all sites and corrected copies were put into effect for the conduct of the trial.

The Protocol 49653/011 sample informed consent contained the basic elements of informed consent (§50.25 (a)) as well as additional elements of informed consent (§50.25(a)(2)) describing any reasonably foreseeable risks or discomforts to the subject. The symptoms of hypoglycemia were explicitly described and emphasized, as this was found to be a problem associated with earlier classes of antidiabetes compounds (i.e. sulfonylureas). The SB sample informed consents

How is this a typographical error?

Did they mean to type 'placebo'?

but mistakenly typed glibenclamide



are rarely, if ever, accepted without change. In the case of Protocol 49653/011, all but two IRB committees edited the sample document to strengthen the risk language, particularly for potential worsening of disease or hyperglycemia.

At the 27 sites overseen by [REDACTED] information was added (italicized text) to expand the explanation of a placebo-controlled trial:

If you agree to take part, you will be randomly assigned (like the toss of a coin) to take a fixed dose of BRL 49653C or placebo (an inactive substance). Neither you nor your study doctor will know whether you are receiving BRL 49653C or placebo; however, this information is available to the study doctor if needed in an emergency."

The sample informed consent of SB had included the note: "There is no guarantee that you will benefit by participating in this study." The [REDACTED] strengthened this language by adding: "*Your condition may not improve or may worsen while participating in the study.*"

At the 16 sites covered primarily by university IRBs, similar language was added to consent documentation. The language which follows is directed toward placebo use and the risk of increased blood sugar. [REDACTED] IRB of [REDACTED] added: "*If your blood sugar is too high you may experience an increase in thirst, hunger or increased urination.- If severe, high blood sugar can cause coma and death. If such blood sugar changes last, the study doctor may remove you from the study so that you can be treated with medication chosen by your own doctor.*" Please refer to Attachment 1 for additional examples of IRB additions directed toward placebo use in type 2 diabetes mellitus patients.

Recognizing that the responsibility for the patient, as a human subject involved in biomedical research, must always rest with a medically qualified person, and never rest on the subject of the research, even though the subject has given his or her consent [World Medical Association Declaration of Helsinki], SmithKline Beecham was careful to make provision in the protocol for physician judgement. With regard to blood glucose levels, withdrawal for 'lack of efficacy' included any increase in FPG deemed by the investigator to represent a safety risk, or 2 consecutive visit FPG levels ≥ 300 mg/dL as well as provision that patients could be withdrawn if additional therapy is required to manage their diabetes.

Further, inclusion & exclusion criteria allowed only non-insulin dependent diabetes mellitus patients (non ketosis prone per the National Diabetes Data Group definition), with no history of ketoacidosis to be enrolled. Diet control was built into the protocol and individualized for patients in active and placebo groups. Diabetic diet instruction was provided by a registered dietitian or other qualified professional, consistent with recommendations of the Committee on Food and Nutrition of the American Diabetes Association. Within Protocol 49653/011 there is

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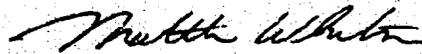
Letter to Dr. Sobel
April 7, 1999
Page 4

evidence that the diet control, monitoring and counseling had an effect. For example, the mean decrease of 0.25% in HbA1C (week 26 vs. screening) in diet only, placebo subgroup, offers evidence of effect of the diet control in maintaining and/or improving glycemic control in these type 2 diabetes mellitus patients over the duration of the trial.

In 1996, SmithKline Beecham designed Protocol 49653/011 in collaboration with endocrinologists and investigators according to the standards of ethical clinical research and accepted medical practice. We believe that the safeguards of the protocol, from patient selection and diet control to withdrawal provisions, were properly placed and implemented to protect the human subjects receiving rosiglitazone or placebo in the trial. Further, the strengthening of risk language in the informed consent documents (by all but 2 IRBs), provides evidence of review and appropriate oversight by the independent IRBs in protecting the rights and safety of the patients.

We trust that the above information and attachments will serve to resolve any concerns that Dr. Misbin and his team have had at any time when reviewing Protocol 49653/011, particularly with respect to adequacy of written informed consent documentation and protection of human subjects. Should there be any additional questions regarding this amendment or subject matter, please do not hesitate to contact me at (610) 917-7250.

Sincerely,



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

Desk copy: Dr. R. Misbin

No where is it stated that patients were informed that withdrawal of antidiabetic medication was part of the study.

IS/ - Among 33 sites, only 2 included added language about ~~placebo~~ withdrawal from active treatment

IS/ [Redacted]

4/20/99

000004



SmithKline Beecham
Pharmaceuticals

Avandia® (rosiglitazone maleate)
NDA 21-071
Amendment to a Pending NDA

April 2, 1999

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

Amendment to a Pending NDA -
Draft Labeling for Sample Cartons and Foils

Dear Dr. Sobel:

Reference is made to the New Drug Application for *Avandia*, NDA 21-071. The NDA provides for use of a novel PPAR γ receptor activator for the treatment of hyperglycemia in type 2 diabetes mellitus, as monotherapy and in combination with metformin.

At this time, we are submitting the color mechanical, draft patient sample cartons and their corresponding foils for review by the FDA team. It is not clear that these items, previously submitted on March 12, 1999, were ever received by the Division. Ms. Jenna Weber informed us today that the chemistry reviewer for NDA 21-071 had not received these items. We apologize for any confusion and hope that the FDA team can review the cartons and foils as rapidly as possible. There is a very long lead time required for printing the cartons.

Other than color changes and minor font changes, which serve to improve the prominence of required label statements, no other changes have been made to the components as they were previously available. We are not submitting components having any graphic representation (known as an "icon"), so review should not be complicated. This submission assures that the final graphic and textual representations on the sample cartons are filed to the NDA. It should be noted that the lot and expiry date will be imprinted onto the edge of the foil blisters, and readable on the side opposite the foil (reverse side).

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Letter to Dr. Sobel

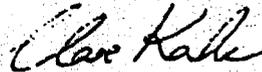
April 7, 1999

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This submission is being made in duplicate. Four (4) copies of the draft labels are submitted to the FDA archival copy, and single copies of the draft labels to all other review copies. Should you have any questions regarding these labels please do not hesitate to contact me at (610) 917-7250.

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Sincerely,



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

Desk copy: Ms. J. Weber

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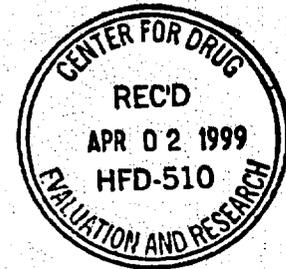
SB
SmithKline Beecham
Pharmaceuticals

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Avandia® (rosiglitazone maleate)
NDA 21-071
Amendment to a Pending NDA

March 31, 1999

Solomon Sobel, M.D.
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852



Amendment to a Pending NDA – 120 day Safety Update

Dear Dr. Sobel:

Submitted herewith, in duplicate, pursuant to section 505(i) of the Federal Food Drug, and Cosmetic Act, and in accordance with 21 CFR 314.50(d)(5)(vi)(b), we are submitting the safety update report 4 months following the initial submission of New Drug Application (NDA) 21-071 on November 24, 1998. The NDA for *Avandia* provides for use of this novel PPAR γ receptor activator for the treatment of hyperglycemia in type 2 diabetes mellitus, as monotherapy and in combination with metformin.

At the time of initial filing, the safety data for all patients receiving *Avandia* for any indication were included in the safety evaluation up to a clinical cut-off date of June 18, 1998. For this 120-day safety update report, the clinical cut-off date is November 7, 1998. The new report summarizes data on 4598 patients exposed to rosiglitazone either as monotherapy or in combination with metformin or sulfonylureas in Phase II/III studies.

Exposure to *Avandia* has increased substantially since the initial filing. Of over 4500 patients exposed to rosiglitazone as monotherapy or in combination with metformin or sulfonylureas in the update report, more than 2000 patients were exposed for at least 12 months compared with 1005 patients at the time of the

Solomon Sobel, M.D.

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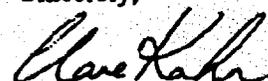
March 31, 1999

NDA. Exposure to sulfonylureas has increased slightly (an additional 100 patients were treated for at least 12 months) with no change in exposure to either metformin or placebo. When compared with the NDA, patient years of exposure was increased considerably from 2492.8 in the NDA to 3673.0 in the update.

We believe that the additional safety data are fully consistent with the data and conclusions of the initial NDA. Specifically, *Avandia* is safe in the treatment of hyperglycemia in type 2 diabetes mellitus, either as monotherapy or when used in combination with metformin.

Thank you for your kind attention to these data. Should you have any questions regarding this amendment, please do not hesitate to contact me at (610) 917-7250.

Sincerely,



G. Clare Kahn, Ph.D.

Group Director

U.S. Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL