CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021071

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

Items 13/14: Patent Information

Pursuant to the provisions of 21 USC §355 (b) and 21 C.F.R. §314.53, particularly subsections (c) and (d), Applicant herewith submits the following patent information for each patent it believes it reasonably could assert against the manufacture, use or sale by another of certain compositions, formulations or uses of a drug or drug product for which Applicant is submitting this NDA:

Patent I:

(i) Patent No. 5,002,953 expiring 30 August 2008.
(ii) Type of patent: drug, formulation and use.
(iii) Owner: Beecham Group plc.
(iv) The applicant resides and is doing business in the United States.

The undersigned declares that Patent Number 5,002,953 covers the composition (new chemical entity), a formulation and a method of use of rosiglitazone maleate. This product is the subject of this application for which approval is being sought.

Patent II:

(i) Patent No. 5,741,803 expiring 21 April 2015.
(ii) Type of patent: drug, formulation and use.
(iii) Owner: SmithKline Beecham plc.
(iv) The applicant resides and is doing business in the United States.

The undersigned declares that Patent Number 5,741,803 covers the composition (new chemical entity), a formulation and a method of use of rosiglitazone maleate. This product is the subject of this application for which approval is being sought.

EXCLUSIVITY SUMMARY FOR NDA # 21-071 SUPPL # _____

Trade Name AVANDIA Generic Name ROSIGLITAZONE

Applicant Name SKB HFD # 510

Approval Date If Known MAY 25, 1999

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES /✓/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /✓/

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

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

YES /✓/ NO /___/

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

_____

_____

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

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

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

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

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved.

Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product. NOT APPLICABLE

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

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

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

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

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

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

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

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

_____ _____

_____ _____

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

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

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

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

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

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

YES /___/ NO /___/

If yes, explain: _____

_____

/S/ [redacted] 5/20/99
Signature
Title: RHPM

5/20/99
Date

/S/ [redacted]
Signature of [redacted]
Division Director

5/24/99
Date

APPEARS THIS WAY ON ORIGINAL

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21071	**Trade Name:**	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T
Supplement Number:		**Generic Name:**	ROSIGLITAZONE MALEATE
Supplement Type:		**Dosage Form:**	Tablet; Oral
Regulatory Action:	AP PN	**Proposed Indication:**	For the treatment of patients with Type 2 diabetes mellitus as monotherapy, and in combination with metformin (coadministration)

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION?
NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	-
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JENA WEBER

/S/ [redacted]

Signature Date April 4, 1999

Item 16: Debarment Certification

Pursuant to section 306(K)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that the applicant did not and will not use in any capacity, in connection with this application, the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act.

[redacted] APPEARS THIS WAY ON ORIGINAL

Weber

NDA 21-071

SmithKline Beecham Pharmaceuticals
Attention: Clare Kahn, Ph.D.
Group Director, NARA
1250 South Collegeville Road
Collegeville, PA 19426-0989

MAR 30 1999

Dear Dr. Kahn:

Please refer to your pending November 23, 1998, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avandia™ (rosiglitazone maleate) Tablets.

We also refer to our acknowledgment letter dated December 1, 1998, that stated the drug review priority classification for this application would be standard (S).

Our policy regarding determination of priority or standard review status is based on the proposed indication and alternative treatments marketed for the proposed indication. Upon further consideration of your application, we have concluded that this application should receive a priority review. The user fee goal date is May 25, 1999.

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 10 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.

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

Sincerely,

/S/ [redacted] 3.30.99

for Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

cc:
Archival NDA 21-071
HFD-510/Div. Files
HFD-510/JWeber
HFD-510/RMisbin/SMalozowski/HRhee/RSteigerwalt/XYsern/SMoore/JMele/TSahlroot/
RShore/HYAhn
DISTRICT OFFICE

Drafted by: JMW/March 30, 1999
Initialed by:EGAlliers 3/3/S/ [redacted]
final: Jweber 3/30/99
filename: N21071.ACK

GENERAL CORRESPONDENCE DDR: Change drug priority classification in COMIS to priority.

[redacted]

Information Request
Office of Clinical Pharmacology and Biopharmaceutics
NDA 21-071 Rosiglitazone

2/23/99

1) For Studies 49653/011 and 49653/020 (rosiglitazone arm only), please provide the following:

- A plot of ΔHgb_{A1c} from baseline at Week 26 as a function of rosiglitazone clearance. The individual data points should be identified as male or female. For Study 020, the population PK model should be used to estimate the individual patient clearances. (estimates for Study 011 already exist). Each study should be plotted separately, as well as combined on one plot.

- A plot of ΔHgb_{A1c} from baseline at Week 26 as a function of rosiglitazone AUC. The individual data points should be identified as male or female. For both studies, the population PK model should be used to estimate the individual patient AUCs. Each study should be plotted separately, as well as combined on one plot.

- A plot of ΔFPG from baseline at Week 26 as a function of rosiglitazone clearance. The individual data points should be identified as male or female. For Study 020, the population PK model should be used to estimate the individual patient clearances. (estimates for Study 011 already exist). Each study should be plotted separately, as well as combined on one plot.

- A plot of ΔFPG from baseline at Week 26 as a function of rosiglitazone AUC. The individual data points should be identified as male or female. For both studies, the population PK model should be used to estimate the individual patient AUCs. Each study should be plotted separately, as well as combined on one plot.

Please submit these plots (eight in all) in Excel format, as well as hard copies.

/S/ [redacted]

Cleared for faxing

Rae-Young Ahn, Ph.D.

[redacted]

Weber

NDA 21-071

DEC - 1 1998

SmithKline Beecham Pharmaceuticals
Attention: G. Clare Kahn, Ph.D.
Group Director, NARA
1250 South Collegeville Road
Mail Code UP4340, PO Box 5089
Collegeville, PA 19426-0989

Dear Dr. Kahn:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Avandia (rosiglitazone maleate) Tablets, 2, 4, 8 mg
Therapeutic Classification:	Standard (S)
Date of Application:	November 24, 1998
Date of Receipt:	November 25, 1998
Our Reference Number:	NDA 21-071

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 January 24, 1999, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be September 25, 1999, and the secondary user fee goal date will be November 25, 1999.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

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

Sincerely yours,

/S/ [redacted] 11.30.98

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

cc:
Archival NDA 21-071
HFD-510/Div. Files
HFD-510/J. Weber
HFD-510/S.Moore
HFD-510/R.Steigerwalt
HFD-510/S.Malozowski
DISTRICT OFFICE

APPEARS THIS WAY ON ORIGINAL

Drafted by: emg/November 30, 1998
final:
filename: N21071AC.NDA

ACKNOWLEDGEMENT (AC)

SmithKline Beecham
Pharmaceuticals

May 21, 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

Response to FDA Request for Information:
Submission of Container and Carton Labels

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 May 21, 1999 telephone call from Ms. Jena Weber requesting SB to fax and submit copies of final container and carton labels to the NDA file. As discussed with Ms. Weber, not all of these labels have been printed yet. For those which have not been printed, we are providing the final vendor proof copy, which will be used to print the final labels.

Attached with this letter are 2 copies of these labels for FDA archives. A desk copy of this submission is also enclosed for Ms. Weber. Simultaneously, we are submitting the container and carton labeling by facsimile. 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

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

Desk Copy: Ms. Jena Weber, HFD-510

000001

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