CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-071/001

ADMINISTRATIVE DOCUMENTS

Item 14: Patent Certification

APPEARS THIS WAY
ON ORIGINAL

SmithKline Beecham
Pharmaceuticals

February 11, 2000

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg. rm. 2-14
12420 Parklawn Dr.
Rockville, MD 20857

Re: SNDA 21-071/S-001 Patent Information

Dear Sirs:

In accordance with 21 C.F.R. 314.53(d)(4), SB submits the following patent information relating to the subject supplemental NDA.

Pat. No.	Expiration Date	Type of Patent	Patent Owner	Representative of Patent Owner
5,002,953	August 30, 2008	drug/drug product composition method of use	SmithKline Beecham Corporation	Charles M. Kinzig, Corporate Intellectual Property - UW2220, SmithKline Beecham Corporation 709 Swedeland Road King of Prussia, PA 19406

The undersigned declares that U.S. Patent Number 5,002,953 covers the composition and method of use of *Avandia* (rosiglitazone maleate). This product is the subject of this application for which approval is being sought.

This letter is being submitted in duplicate.

Very truly yours,

Sharon W. Shapowal

Sharon W. Shapowal

000055

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

Item 13: Patent Information

Patent 1

Pat. No.	Expiration Date	Type of Patent	Patent Owner	Representative of Patent Owner
5,002,953	August 30, 2008	drug/drug product composition method of use	SmithKline Beecham Corporation	Charles M. Kinzig, Corporate Intellectual Property - UW2220, SmithKline Beecham Corporation 709 Swedeland Road King of Prussia, PA 19406

Patent 2

Pat. No.	Expiration Date	Type of Patent	Patent Owner	Representative of Patent Owner
5,741,803	April 21, 2015	drug/drug product composition method of use	SmithKline Beecham Corporation	Charles M. Kinzig, Corporate Intellectual Property - UW2220, SmithKline Beecham Corporation 709 Swedeland Road King of Prussia, PA 19406

APPEARS THIS WAY
ON ORIGINAL

SmithKline Beecham
Pharmaceuticals

February 11, 2000

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Re: SNDA No. 21-071/S-001 Patent Information

Dear Sirs:

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Pat. No.	Expiration Date	Type of Patent	Patent Owner	Representative of Patent Owner
5,741,803	April 21, 2015	drug/drug product composition method of use	SmithKline Beecham Corporation	Charles M. Kinzig, Corporate Intellectual Property - UW2220, SmithKline Beecham Corporation 709 Swedeland Road King of Prussia, PA 19406

The undersigned declares that U.S. Patent Number 5,741,803 covers the composition and method of use of *Avandia* (rosiglitazone maleate). This product is the subject of this application for which approval is being sought.

This letter is being submitted in duplicate.

Very truly yours,

Sharon W. Shapowal

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EXCLUSIVITY SUMMARY FOR NDA # 21-071 SUPPL # 001

Trade Name Avandia Generic Name Rosiglitazone

Applicant Name SKB HFD # 510

Approval Date If Known _____

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.) SE1

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:

_____

_____

Form OGD-011347 Revised 10/13/98
cc: Original NDA Division File HFD-93 Mary Ann Holovac

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 /__/

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

NDA# 21-071 Avandia

NDA# _____ _____

NDA# _____ _____

2. Combination product.

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:

SNDA 079 & SNDA 015

SNDA 096

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 /✓/

" #3 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 /✓/

" #3 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"):

SNDY 079 SNDY 015 (Europe)

SNDY 096 _____

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: _____

Investigation #3 ND ✓ Study 015 was conducted in Europe by the applicant without a U.S. IND.

(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 /X/

If yes, explain: _____

_____

/S/ 3/20/00 & 8/24/99
Signature Date
Title: CMO M

/S/ 3/30/00
Signature of Office/ Date
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

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:	1	**Generic Name:**	ROSIGLITAZONE
Supplement Type:	SE1	**Dosage Form:**	TAB
Regulatory Action:	PN	**Proposed Indication:**	Provides for the use of Avandia (rosiglitazone maleate) tablets in combination with sulfonylurea for the treatment of type 2 diabetes mellitus.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

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	Inadequate for ALL pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

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

COMMENTS:

WR letter issued 2/1/00; age group of pediatric patients to be recruited will be 8 - 16 years of age.

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

/S/ 3/30/00 (updated)

Signature Date

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.

- APR - 3 2000

MEMORANDUM

DATE: April 2, 2000

/S/ 4/3/00

FROM: John K. Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products
Director, Office of Drug Evaluation II

TO: NDA 21-071/S-001

SUBJECT: Overview of Supplemental NDA Review Issues

Administrative

S-001 was submitted by SmithKline Beecham to NDA 21-071 for Avandia (rosiglitazone maleate) Tablets on June 4, 1999. This supplemental application provides for the addition of the indication for use of Avandia in combination with a sulfonylurea in patients with Type 2 diabetes mellitus when diet and exercise and a sulfonylurea does not achieve adequate glycemic control. This supplemental application was assigned a standard review. The 10-month user fee goal date for this application is April 3, 2000.

Clinical/Statistical

In support of the additional indication, the sponsor submitted three randomized, double-blind, placebo-controlled studies in which rosiglitazone or placebo was added to existing sulfonylurea therapy in patients not adequately controlled on a sulfonlyurea (and in some patients other antidiabetic medications) alone. Please refer to the medical review prepared by Dr. Misbin and the statistical review prepared by Ms. Mele for a more detailed analysis of these studies. I concur with Dr. Misbin and Ms. Mele that these studies have adequately demonstrated that rosiglitazone is safe and effective when used in combination with a sulfonylurea. As was seen in the previously reviewed studies for combination therapy of rosiglitazone and metformin, patients inadequately treated with the maximum dose of a sulfonylurea at baseline who were randomized to receive rosiglitazone alone during the controlled portion of the clinical trial demonstrated a loss of glycemic control. The pattern of adverse events associated with rosiglitazone in combination with a sulfonylurea were generally similar to those seen in prior studies with rosiglitazone or those commonly associated with sulfonylureas. The lipid effects seen with rosiglitazone therapy along with the anemia, edema, and possible increase in CHF remain of concern with regard to the long-term outcome of patients. The sponsor is conducting a long-term outcomes study in patients treated with rosiglitazone as part of a Phase 4 commitment of the original approval of this NDA that may help to address these concerns.

This supplemental NDA is approvable from a clinical/statistical perspective pending agreement with the sponsor on adequate labeling (see below).

Pharm/Tox, CMC, Clinical Pharmacology/Biopharmaceutics
No new data were included in the submission for any of these disciplines.

Data Integrity
The Division of Scientific Investigations conducted audits of four clinical sites involved in the conduct of the pivotal studies submitted in support of the new indication. The final audit results were NAI for three sites and VAI for one site. The deficiencies noted at the site rated as VAI were minor and unlikely to have impacted on the integrity of the data generated by that site. These audits do not suggest any concerns related to the integrity of the database submitted in support of this supplement.

Labeling
There are various minor edits that need to be made to the draft labeling submitted by the sponsor on March 30, 2000, before this supplement can be approved. The labeling comments will be negotiated with the sponsor prior to issuance of a final action letter.

The labeling for Avandia also warrants updating to better reflect the current state of knowledge following approximately 9 months of marketing in the U.S. In particular, comments based on postmarketing reports of liver toxicity in patients treated with Avandia need to be added. Also, the labeling currently refers to two "ongoing" cardiac safety studies. This section of the labeling should be updated if either or both of these studies is (are) now completed. The sponsor will be asked to submit a labeling supplement within 30 days of approval of this supplement to accomplish these updates.

Recommendation
This supplemental application should be APPROVED once satisfactory labeling is negotiated with the sponsor. The sponsor will be asked to submit a labeling supplement within 30 days of the approval of the current supplement to update certain sections of the current label.

cc:

HFD-510/Division File
HFD-510/Jenkins
HFD-510/Weber