CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021073

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

Item 13. Patent Information

21 CFR 314.50 (h) PATENT INFORMATION
ACTOS (PIOGLITAZONE HCl – AD-4833) TABLETS

The following two patents were issued for AD-4833. The drug product name for this chemical entity will be ACTOS (pioglitazone HCl) tablets.

21 CFR 314.53 (c)(i); (ii); (iii); (iv)

US Patent Number	Expiration Date	Type of Patent	Patent Owner	US Representative
4,444,779	July, 27, 1999	drug, drug product	Takeda Chemical Industries, Ltd.	Takeda America Research and Development Center, Inc.
4,687,777	January 17, 2006	drug, drug product	Takeda Chemical Industries, Ltd.	Takeda America Research and Development Center, Inc.

Attached are copies of the front and claim pages of US Patent Numbers 4,444,779 and 4,687,777.

14.0 Patent Certification

Reference is made to the subject NDA for Actos™ (pioglitazone hydrochloride) tablets for the management of type 2 diabetes and the requirements of 505(b)(1) of the Federal Food, Drug and Cosmetic Act as amended and 21 CFR 314.50(c)(2).

Declaration under 21 CFR 314.53(c)(2)

The applicant declares that Patent No. US 4,444,779 and Patent No. US 4,687,777 cover the drug pioglitazone hydrochloride, the drug product pioglitazone hydrochloride tablets, 15 mg, 30 mg, and 45 mg and its method of use.

This product is the subject of this application for which approval is sought.

As provided for under the Patent Term Restoration Act, Takeda America Research & Development Center, Inc. will be requesting patent term restoration upon receipt of approval of pioglitazone hydrochloride.

Exclusivity Checklist

NDA: 21-073
Trade Name: ACTOS
Generic Name: PIOGLITAZONE HYDROCHLORIDE
Applicant Name: TAKEDA
Division: HFD-510 (DMEDP)
Project Manager: JENA WEBER (76422)
Approval Date: JULY , 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 questions about the submission.

a. Is it an original NDA? 1P	(Yes)	No
b. Is it an effectiveness supplement?	Yes	(No)
c. If yes, what type? (SE1, SE2, etc.)		
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.

Explanation:

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:

Explanation:

d. Did the applicant request exclusivity?	Yes	(No)
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?		

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

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?	Yes	(No)
If yes, NDA #		
Drug Name:		

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

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 (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.		Yes		No
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).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.		Yes		No
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).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. 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.				
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. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				
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 BLOCKS.**				
Basis for conclusion:				
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:

Investigation #1, Study #:	
Investigation #2, Study #:	
Investigation #3, Study #:	

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	
Investigation #3	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:

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

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	
Investigation #3	Yes		No	

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

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

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"):

Investigation #1	
Investigation #2	
Investigation #3	

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	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
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		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
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:				

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Signature of PM/CSO
Date: /S/ [redacted] 6/22/99

Signature of Division Director
Date: /S/ [redacted] 6/30/99

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

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Edit Pediatric Information for this Submission

/S/ [redacted]

User Information

Preparer	JENA WEBER
Title	PROJECT MANAGER/CONSUMER SAFETY OFFICER
Division	HFD-510

Application Information

Application Number	21073
Application Clock Date	Jan 15, 1999
Application Type	N
Applicant Sponsor	TAKEDA AMERICA
Drug Trade Name	ACTOS (PIOGLITAZO TABS
Drug Generic Name	PIOGLITAZONE HCL
(leave supplement number, date and type blank, if original ap	
Supplement Number	0
Regulatory Action	PN Pending
Proposed Indication	Developed to improve the glycem Type 2 diabetes.
Has Proposed Indication been Approved?	☐ Check if YES
Adequacy of Proposed label for Pediatric Dosing	
Is there a Pediatric Phase 4 Commitment in the Action Letter for the Original Submission?	☒ Check if YES
Comments & Recommendations (please date)	□□□□
Is there Pediatric Content?	○ Yes ◉ No

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APPEARS THIS WAY ON ORIGINAL

16.0 Debarment Certification

A Debarment Certification as specified by the Generic Drug Enforcement Act of 1992 is provided.

APPEARS THIS WAY ON ORIGINAL

Takeda America Research and Development Center, Inc.
Princeton, NJ

NDA 21-073
Actos™
(Pioglitazone HCl) Tablets

Certification of Compliance with the Generic Drug Enforcement Act

In compliance with the Generic Drug enforcement Act of 1992, Takeda America Research and Development Center, Inc. certifies that we did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)] in connection with this application.

M. Obayashi

Mikihiko Obayashi, Ph.D.
President,
Takeda America Research and Development Center, Inc.

Dec. 31. 1998
Date

APPEARS THIS WAY ON ORIGINAL

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Takeda America Research and Development Center, Inc.
Princeton, NJ

NDA 21-073
Actos™
(Pioglitazone HCl) Tablets

Certification Statement
as requested by the
Generic Drug Enforcement Act of 1992

In compliance with the Generic Drug Enforcement Act of 1992, Covance certifies that we did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) of Section 306 of the Food, Drug and Cosmetic Act in connection with this application.

Patricia Young, Ph.D.
Vice President, Regulatory Affairs
Vice President, Corporate Compliance

1st December 1998
Date

APPEARS THIS WAY ON ORIGINAL

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TAKEDA AMERICA RESEARCH AND DEVELOPMENT CENTER, INC.
Princeton, NJ

ACTOS®
(pioglitazone HCl tablets)

CERTIFICATION OF COMPLIANCE WITH THE GENERIC DRUG ENFORCEMENT ACT

In compliance with the Generic Drug Enforcement Act of 1992, [redacted] certifies that we did not use in any capacity the services of any person debarred under subsection (a) or (b) of Section 306 of the Food, Drug, and Cosmetic Act, in connection with this application.

/S/ [redacted]

15 Jul 98
DATE

FOR [redacted]

/S/ [redacted]

PRINT NAME

APPEARS THIS WAY ON ORIGINAL

TAKEDA AMERICA RESEARCH AND DEVELOPMENT CENTER, INC.
Princeton, NJ

ACTOS®
(pioglitazone HCl tablets)

CERTIFICATION OF COMPLIANCE WITH THE GENERIC DRUG ENFORCEMENT ACT

In compliance with the Generic Drug Enforcement Act of 1992, [redacted] certifies that we did not use in any capacity the services of any person debarred under subsection (a) or (b) of Section 306 of the Food, Drug, and Cosmetic Act, in connection with this application.

/s/ [redacted]

July 17, 1998
DATE

FOR [redacted]

/s/ [redacted]

PRINT NAME

TAKEDA AMERICA RESEARCH AND DEVELOPMENT CENTER, INC.
Princeton, NJ

ACTOS®
(pioglitazone HCl tablets)

CERTIFICATION OF COMPLIANCE WITH THE GENERIC DRUG ENFORCEMENT ACT

In compliance with the Generic Drug Enforcement Act of 1992, [redacted] certifies that we did not use in any capacity the services of any person debarred under subsection (a) or (b) of Section 306 of the Food, Drug, and Cosmetic Act, in connection with this application.

/S/ [redacted]

FOR [redacted]

7/15/98
DATE

/S/ [redacted]

PRINT NAME

APPEARS THIS WAY ON ORIGINAL

JUL 15 1998

TAKEDA AMERICA RESEARCH AND DEVELOPMENT CENTER, INC.
Princeton, NJ

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CERTIFICATION OF COMPLIANCE WITH THE GENERIC DRUG ENFORCEMENT ACT

In compliance with the Generic Drug Enforcement Act of 1992, [redacted] certifies that we did not use in any capacity the services of any person debarred under subsection (a) or (b) of Section 306 of the Food, Drug, and Cosmetic Act, in connection with this application.

[redacted]

FOR [redacted]

[redacted]

PRINT NAME

6 AUGUST 1998
DATE