



TAKEDA AMERICA RESEARCH &amp; DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207  
PRINCETON, NEW JERSEY 08540  
TEL: (609) 452-1113 • FAX: (609) 452-121805 April, 1999  
Ref: 040501SR

Solomon Sobel, M.D., Director  
Division of Metabolic & Endocrine Drug Products (HFD-510)  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Document Control Room #14B-19  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

DESK COPY

NDA No. 21-073  
Pioglitazone HCl (AD-4833) Tablets  
NDA Amendment: # 008

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above.

In our submission to the Division on 31 March, 1999 (NDA Amendment #007), we submitted several documents including Attachment 5 which contained the tables of precision and accuracy values of the analytical assay used to measure pioglitazone and metabolites. [REDACTED]

If you have any questions concerning this submission, please contact me at (609) 452-1113, extension 4403.

Sincerely,

Stephanie Rais  
Regulatory Consultant for  
Takeda America Research and Development Center, Inc.

Enclosure: Form FDA 356h

Cc: Dr. James Wei, Biopharmaceutics Reviewer (DESK COPY, Submission)  
Ms. Jena Weber, Project Manager (DESK COPY, Letter Only)





TAKEDA AMERICA RESEARCH &amp; DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207  
PRINCETON, NEW JERSEY 08540  
TEL: (609) 452-1113 • FAX: (609) 452-121831 March, 1999  
Ref: 033101SR

Solomon Sobel, M.D., Director  
Division of Metabolic & Endocrine Drug Products (HFD-510)  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Document Control Room #14B-19  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

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**NDA No. 21-073**  
**Pioglitazone HCl (AD-4833) Tablets**  
**NDA Amendment: # 006**

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above.

In response to a request from Dr. James Wei, Biopharmaceutics Reviewer (Facsimile dated 12 March, 1999), Takeda America Research and Development Center, Inc. has converted the information listed below into electronic PDF files, which are contained in the enclosed CD-ROM.

This amendment represents the formal submission of the following electronic documents; 1) the ACTOS Package Insert, 2) the annotated Package Insert; 3) the Section 6 summary (Human Pharmacokinetics and Bioavailability, and 4) the individual study summaries in Section 6. These documents were originally submitted in Takeda America Research and Development Center, Inc.'s original New Drug Application (NDA No. 21-073) on 15 January, 1999 (#000).

If you have any questions concerning this submission, please contact me at (609) 452-1113, extension 4409.

Sincerely,

Stephanie Rais  
Regulatory Consultant for  
Takeda America Research and Development Center, Inc.

Enclosure: Form FDA 356h

Cc: Dr. James Wei, Biopharmaceutics Reviewer (DESK COPY, Letter Only)  
Ms. Jena Weber, Project Manager (DESK COPY, Letter Only)





TAKEDA AMERICA RESEARCH &amp; DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207  
PRINCETON, NEW JERSEY 08540  
TEL: (609) 452-1113 • FAX: (609) 452-121831 March, 1999  
Ref: 033102SR

Solomon Sobel, M.D., Director  
Division of Metabolic & Endocrine Drug Products (HFD-510)  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Document Control Room #14B-19  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

**NDA No. 21-073**  
**Pioglitazone HCl (AD-4833) Tablets**  
**NDA Amendment: # 007**

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above. (Please Note: This is Amendment number 7. Amendment number 6 is an electronic submission of biopharmaceutics data. Amendment 6 has been sent to Central Document Room, 12229 Wilkins Ave.)

In response to a request from Dr. Jim Wei (facsimile dated 12 March 1999), Takeda America Research and Development Center, Inc. is submitting the below-listed information as requested.

Included in this amendment are the following:

- repeated dissolution studies,
- pH profile,
- a cross-reference table listing the lots of drug product used in the clinical trials,
- tables of precision and accuracy values of the analytical assay used to measure pioglitazone and metabolites.

Further details about the submission appear in an introductory document that follows FDA Form 356H. If you have any questions concerning this submission, please contact the undersigned at (609) 452-1113, extension 4403.

Sincerely,

Stephanie Rais  
Regulatory Consultant for  
Takeda America Research and Development Center, Inc.

Enclosure: Form FDA 356h

Cc: Dr. James Wei, Biopharmaceutics Reviewer (DESK COPY, Submission)  
Ms. Jena Weber, Project Manager (DESK COPY, Letter Only)





TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207  
PRINCETON, NEW JERSEY 08540  
TEL: (609) 452-1113 • FAX: (609) 452-1218

DESK COPY

29 March, 1999  
Ref: 032901SR

Solomon Sobel, M.D., Director  
Division of Metabolic & Endocrine Drug Products (HFD-510)  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Document Control Room #14B-19  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857



**NDA No. 21-073**  
**Pioglitazone HCl (AD-4833) Tablets**  
**NDA Amendment: # 005**

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above.

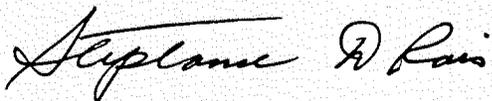
We are submitting the enclosed echocardiographic data based on an agreement reached with the Division during a teleconference between Takeda America Research and Development Center, Inc. and Dr. Misbin, Medical Reviewer, on November 6, 1998 which was also noted in the cover letter for Takeda's original NDA (#21-073) submitted on January 15, 1999 (#000).

Volume 1 contains Addendum A to Report No. AD-4833/PNFP-001.6. Volume 2 and 3 contain Addendum A to Report No. AD-4833/PNFP-011.2. These addenda contain echocardiographic findings. (The appendices contained in these reports are numbered 13, which is a direct continuation from the full clinical reports submitted in the original NDA, which ended with Appendix 12.)

If there are any additional questions, or if any FDA staff would like to discuss the matter further, please do not hesitate to contact either Dr. Schneider or the undersigned at (609) 452-1113, extension 4403.

Dr. Solomon Sobel  
032901SR  
Page -2-

Sincerely yours,



Stephanie Rais  
Regulatory Consultant for  
Takeda America Research and Development Center, Inc.

Enclosure: Form FDA 356h (submitted in duplicate)

Cc: Dr. Misbin (DESK COPY)  
Ms. Jena Weber (DESK COPY)

APPEARS THIS WAY ON ORIGINAL



DUPLICATE

BEST POSSIBLE COPY

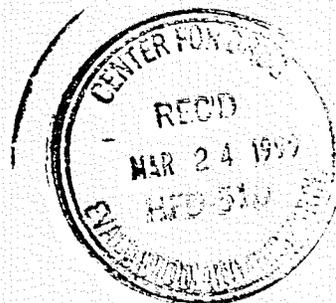
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TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207  
PRINCETON, NEW JERSEY 08540  
TEL: (609) 452-1113 • FAX: (609) 452-1218

23 March, 1999  
Ref: 032302SR

Solomon Sobel, M.D., Director  
Division of Metabolic & Endocrine Drug Products (HFD-510)  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Document Control Room #14B-19  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857



**NDA No. 21-073**  
**Pioglitazone HCl (AD-4833) Tablets**  
**NDA Amendment: # 004**

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above. (Please Note: This is Amendment number 4. Amendment number 3 is an electronic submission of preclinical data. Amendment 3 has been sent to Central Document Room, 12229 Wilkins Ave.)

As a result of the teleconference that took place on Friday, March 19, 1999 between Dr. Malozowski, Dr. Misbin and Ms. Weber of FDA and Dr. Schneider and Ms. Rais for Takeda America Research & Development Corp. (TAR&DC), we are enclosing color graphs showing the results from Monotherapy Study 001 and Monotherapy Study 026.

The attachments contain figures showing the results for HbA1c and fasting blood glucose obtained during screening, at baseline, and throughout the double-blind portion of each study. The first figure in each group presents data for all patients combined. The remainder of the figures represents the different subgroups e.g., naïve, previously treated FBG < 280 mg/dl at baseline, etc. Legends are listed at the bottom of each figure and are in color for easy visual identification. For some patient subgroups, the difference from placebo is marked to the right of the figure. Attachments 1 and 2 contain the figures showing the results from Study 001 for HbA1c and fasting blood glucose, respectively



Dr. Solomon Sobel  
Ref.: 032302SR  
Page -2-

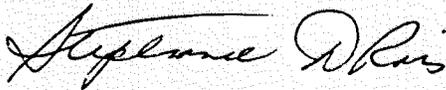
for the 45 mg dose group. Attachments 3 and 4 contain results from Study 026 for HbA1c and fasting blood glucose, respectively for the 30 mg dose group.

These results indicate that in previously treated patients with blood glucose values <280 mg/dl at baseline, pioglitazone HCl at doses of 30 mg (Study 026) or 45 mg (Study 001) is effective and these patients return to baseline values during the treatment period. These figures are provided for purposes of clarification because the data, while contained in the NDA supplemental reports, were not graphically displayed.

Per our agreements made during the teleconference, the previously treated patient subgroup data presented in this submission will not be presented at the Advisory Committee Meeting. As you requested, TAR&DC will present data on naïve patients only. As we agreed, there is adequate data from naïve patients to support NDA approval. As we also discussed, safety data from all patients will be presented at the meeting.

If there are any additional questions, or if any FDA staff would like to discuss the matter further, please do not hesitate to contact either Dr. Schneider or the undersigned at (609) 452-1113, extension 4403.

Sincerely yours,



Stephanie Rais  
Regulatory Consultant for  
Takeda America Research and Development Center, Inc.

Enclosure: Form FDA 356h (submitted in duplicate)

Cc: Dr. Misbin (DESK COPY)



TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

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PRINCETON, NEW JERSEY 08540  
TEL: (609) 452-1113 • FAX: (609) 452-1218



23 March, 1999  
Ref: 032301SR

Solomon Sobel, M.D., Director  
Division of Metabolic & Endocrine Drug Products (HFD-510)  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Document Control Room #14B-19  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

**NDA No. 21-073**  
**Pioglitazone HCl (AD-4833) Tablets**  
**NDA Amendment: # 003**

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above.

In response to Dr. Herman Rhee's request that the toxicology reports (text, figures and summary tables) be provided electronically, Takeda America Research and Development Center, Inc. has had the second set of toxicology reports converted to electronic PDF files which are contained on the enclosed CR-ROM. The enclosed CD-ROM contains the reproductive toxicology studies and the mutagenicity and genotoxicity studies. All of the reports contained on the enclosed CD-ROM were originally submitted in Takeda's New Drug Application (NDA #21-073), submitted on January 15, 1999 (#000).

This is the second CD-ROM to be submitted with preclinical reports. The third CD in the preclinical series will contain the remainder of the toxicology studies (i.e., the acute and sub-chronic study reports, figures and summary tables).

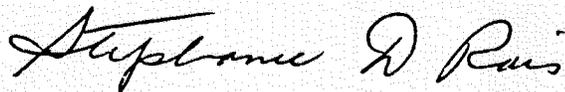


Dr. Solomon Sobel  
Ref.: 032301SR  
Page -2-

Takeda America Research and Development Center, Inc. has been informed by Dr. Randy Levin that these electronic documents, originally submitted in NDA #21-073, must be forwarded, as an NDA amendment in order to have the enclosed CD-ROM uploaded to Dr. Herman Rhee.

If you have any questions concerning this submission, please contact me at (609) 452-1113, extension 4409.

Sincerely,



Stephanie Rais  
Regulatory Consultant for  
Takeda America Research and Development Center, Inc.

Enclosure: Form FDA 356h (submitted in triplicate)

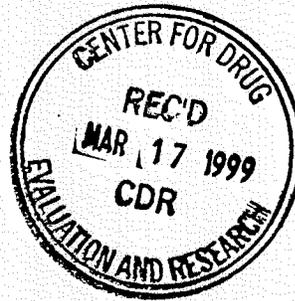
Cc: Dr. Herman Rhee (DESK COPY - cover letter only)  
Ms. Jena Weber (DESK COPY cover letter only)



TAKEDA AMERICA RESEARCH &amp; DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207  
PRINCETON, NEW JERSEY 08540  
TEL: (609) 452-1113 • FAX: (609) 452-1218

## DESK COPY

16 March, 1999  
Ref: 031601SR

Solomon Sobel, M.D., Director  
Division of Metabolic & Endocrine Drug Products (HFD-510)  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Document Control Room #14B-19  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

**NDA No. 21-073**  
**Pioglitazone HCl (AD-4833) Tablets**  
**NDA Amendment: # 002**

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above.

In response to Dr. Herman Rhee's request that the toxicology reports (text, figures and summary tables) be provided electronically, Takeda America Research and Development Center, Inc. has converted several toxicology reports to electronic PDF files which are contained on the enclosed CR-ROM. The enclosed CD-ROM is one of potentially three CDs that will be submitted. This CD contains the one-year chronic toxicology studies (in rats, dogs, and monkeys), the carcinogenicity studies (in mice and rats), and special studies. All of the reports contained on the enclosed CD-ROM were originally submitted in Takeda's New Drug Application (NDA #21-073), submitted on January 15, 1999 (#000).

As agreed with Dr. Rhee, we have begun processing electronic documents with the most important studies. The next CD will provide electronic versions of the reproductive toxicology studies and the mutagenicity and genotoxicity studies. The third CD in the preclinical series will contain the remainder of the toxicology studies.

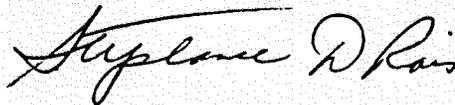


Dr. Solomon Sobel  
Ref.: 031601SR  
Page -2-

Takeda America Research and Development Center, Inc. has been informed by Dr. Randy Levin that these electronic documents, originally submitted in NDA #21-073, must be forwarded, as an NDA amendment in order to have the enclosed CD-ROM uploaded to Dr. Herman Rhee.

If you have any questions concerning this submission, please contact me at (609) 452-1113, extension 4409.

Sincerely,

A handwritten signature in cursive script that reads "Stephanie Rais".

Stephanie Rais  
Regulatory Consultant for  
Takeda America Research and Development Center, Inc.

Enclosure: Form FDA 356h (submitted in triplicate)

Cc: Dr. Herman Rhee  
Ms. Jena Weber

ORIGINAL BC

ERICA RESEARCH & DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207  
PRINCETON, NEW JERSEY 08540  
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ORIG AMENDMENT

02 March, 1999  
Ref: 030201SR

Solomon Sobel, M.D., Director  
Division of Metabolic & Endocrine Drug Products (HFD-510)  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Document Control Room #14B-19  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857



NDA No. 21-073  
Pioglitazone HCl (AD-4833) Tablets  
NDA Amendment: # 001

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above.

As noted in the NDA (submitted on 1/15/99, Original Submission #000) Section 4.A.3.8.1 (Volume 1.006, page 001), we are submitting stability results for ACTOS™ tablets made according to commercial conditions. Data is provided for three (3) commercial lots of each strength.

Included in this submission you will find: 1) A summary of the stability of Drug Product; 2) A-35-1071; 3) A-35-1072; 4) A-35-1073; and 5) Tables 1 through 3, which supplement the final reports.

If you have any questions concerning this submission, please contact me at (609) 452-1113, extension 4409.

Sincerely,

Stephanie Rais  
Regulatory Consultant for  
Takeda America Research and Development Center, Inc.

Enclosure: Form FDA 356h (submitted in triplicate)

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

Attachment 1

Attachment 2

Attachment 3

Attachment 4

Attachment 5



TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207  
PRINCETON, NEW JERSEY 08540  
TEL: (609) 452-1113 • FAX: (609) 452-1218

15 January, 1999  
Ref: 011501MO

Solomon Sobel, M.D., Director  
Division of Metabolic & Endocrine Drug Products (HFD-510)  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Document Control Room #14B-19  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

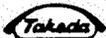
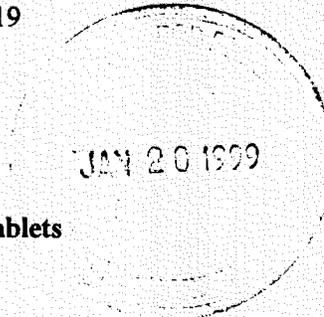
NDA No. 21-073  
Pioglitazone HCl (AD-4833) Tablets  
Original Submission: # 000

Dear Dr. Sobel:

Pursuant to section 505 (b) of the Federal Food and Cosmetic Act and 21 CFR 314.50, Takeda America Research and Development Center, Inc. herewith submits our original New Drug Application for ACTOS™ (pioglitazone hydrochloride) Tablets. Takeda America would like to request a priority review of this application based on the discussions at a meeting with the Division's medical reviewers on July 13, 1998 at which the Division indicated that it would consider a priority review designation based on the efficacy and safety information.

ACTOS™ Tablets is a solid oral dosage form developed to improve glycemic control in patients with Type 2 diabetes (Non-Insulin Dependent Diabetes Mellitus, NIDDM). An extensive clinical development program has been conducted in the United States, Japan and Europe. The clinical studies in the US have been conducted under Takeda America Research and Development Center, Inc.'s Investigational New Drug Application, # 33,729.

The clinical program for this NDA is comprised of twenty-four (24) completed clinical pharmacology studies, eleven (11) completed controlled clinical studies including three (3) US pivotal studies of ACTOS™ as monotherapy and three (3) US pivotal studies of ACTOS™ in combination with another therapeutic agent, five (5) completed uncontrolled clinical studies, and thirteen (13) ongoing studies.



Dr. Solomon Sobel  
NDA No. 21-073

Page 2  
15 January, 1999

A total of 4,989 individuals (4,501 patients and 488 subjects) were enrolled in the completed studies in this clinical program. Of the 4,989 subjects, 3,752 received pioglitazone as either monotherapy or combination therapy. As of the data cut-off date, approximately 2,000 patients were enrolled in the ongoing clinical studies.

The safety and efficacy data from the six (6) US pivotal studies is robust and compelling. It is concluded that pioglitazone hydrochloride is safe and effective for the treatment of Type 2 diabetes (NIDDM) as described in the proposed Package Circular.



This NDA consists of 704 volumes numbered 1.1 through 1.704 and represents the chemistry, manufacturing and controls, preclinical and clinical experience with the product. For your convenience, the locations of the various sections of the NDA are listed in Attachment I to this letter. This NDA also contains CD-ROMs containing the electronic data sets for the two carcinogenicity studies, as well as CD-ROMs containing electronic data sets for the pivotal US clinical studies and human pharmacokinetics studies the locations of the CD-ROMs are also included in Appendix I.

We consider that the application is complete, and will be filed by the Division's 45-day meeting as described in 21.CFR 314.101. Based on an agreement reached with the Division during a conference call November 6, 1998 between representatives from Takeda and Dr. Misbin, Medical Reviewer, Takeda will submit echocardiographic data as an amendment to the NDA within 60 days of the initial filing (21.CFR 314.60(a)). Takeda also references 21 CFR 314.102(c), which provides for an informal meeting with the reviewers of this NDA, and our interest in such a meeting if it is considered to be mutually beneficial.

We are cognizant of our obligations regarding submission of a 4-month Safety Update according to 21 CFR 314.50(d)(5)(vi). Takeda plans to submit this data at the 4-month time point unless the medical reviewers feel that this is not the optimal/most appropriate time to review such a submission. We would like to discuss with representatives of the Division the timing they would prefer for this submission.

In accordance with the Prescription Drug User Fee Act of 1992, a check in the amount of [REDACTED] was sent to the Mellon Bank LockBox, Mellon Bank, Three Melon Bank Center, 27th Floor (FDA 360909), Pittsburgh, PA 152590001 on [REDACTED].

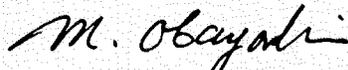
Please note that Takeda America Research and Development Center, Inc. considers this application and all correspondence related thereto as confidential, proprietary, trade secret information and hereby claims protection from disclosure under the applicable sections of 18 USC and Title 21 of the Code of Federal Regulations.

Dr. Solomon Sobel  
NDA No. 21-073

Page 3  
15 January, 1999

Please contact Dr. Scott Grossman of this office, (609) 452-1113, extension 4409, if you have any questions or comments regarding the application.

Sincerely,



Mikihiko Obayashi, Ph.D.  
President

Enclosure: Form FDA 356h