[redacted]

Takeda

..EDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

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

July 7, 1999

NEW CORRESP

NC

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

NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment 19

Dear Dr. Sobel:

The purpose of this Amendment is to provide our official Phase IV commitments

Five formal pharmacokinetic studies including ketaconazole, atorvastatin, nifedipine, fexofenadine and ranitidine will be conducted. Two of these studies are scheduled to commence September 1999.

We also agree to conduct a total of three studies comparing the efficacy and safety of ACTOS 30 mg. versus ACTOS 45 mg in combination with sulfonylurea, metformin and insulin.

In addition, we agree to conduct a study, which will collect information from 1,000 patients treated with ACTOS for 3 years regarding the occurrence of serious liver disease.

We wish to have additional discussion with the Division regarding the issue of conducting a second study in patients with NYHA Class 3 and 4 congestive heart failure in view of our recently proposed labeling revision, (page 18, version July 6, 1999).

We trust this covers the Phase IV commitments discussed with representatives of the Division during recent teleconferences.

Sincerely,

M. Obayashi

Mikihiko Obayashi, Ph.D.
President

takeda

AKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

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

NDA SUPP AMEND
BS

July 6, 1999
Ref: 070301SR

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

NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment 20

Dear Dr. Sobel:

The purpose of this Amendment is to provide official copies of information previously sent to Dr. Pian, NDA Biostatistics Reviewer. On two separate occasions, Dr. Pian was provided with data sent via e-mail from Dr. Annette Mathisen, Director of Biostatistics and Data Management. The data provided to Dr. Pian are contained in this submission in Attachments 1 and 2.

On March 17, 1999, after receiving a request to clarify some data in the submission, Dr. Mathisen provided corrected information to Dr. Pian. The data provided is included in Attachment 1.

In response to a request for additional analyses for lipid variables, additional data tables were provided on April 14, 1999. These tables are contained in Attachment 2.

Please do not hesitate to contact me if you have any questions or if you require clarification of any information.

Sincerely yours,

Stephanie D Rais

Stephanie D. Rais
Regulatory Affairs Consultant for
Takeda America R

Attachment 1

Attachment 2

Takeda

KEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

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

July 2, 1999

NDA SUPP AMEND

BB

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

NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment 18

Dear Dr. Sobel:

The purpose of this Amendment is to provide official copies of information previously sent to Dr. Wei, NDA Reviewer for the Office of Clinical Pharmacology and Biopharmaceutics. On two separate occasions, Dr. Wei was provided with data sent via facsimile. The data provided to Dr. Wei are contained in this submission in Attachments 1 and 2. Furthermore, a change in the dissolution specification for the final product is covered in Attachment 3. This information amends Item 6 of the NDA.

In Attachment 1, data are provided explaining the differences in AUC values noted for some studies in Item 6. Attachment 2 contains an additional analysis and tables in response to Dr. Wei's request for PK/PD modeling.

Furthermore, the dissolution specification for the final product was discussed with Dr. Wei and the specification will be revised to 80% in 30 minutes. Further details are included in Attachment 3. The specification documentation for the tablets is being revised by Takeda Chemical Industries, Ltd., the manufacturer, and will be submitted separately as an Amendment to Item 3 of the NDA.

Please do not hesitate to contact me if you have any questions or if require clarification of any information.

Sincerely yours,

Stephanie D. Rais

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

Takeda

TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

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

ORIGINAL

11 June, 1999
Ref: 061101SR

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

ORIG AMENDMENT
BM

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 14 1999
HFD-510

Re: NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment: # 017

Dear Dr. Sobel:

Pursuant to 21 CFR 314.50, we are hereby amending the above - referenced NDA. At this time we are amending Section 11 (Case Report Tabulations) and Section 12 (Case Report Forms).

On June 3, 1999, we filed Amendment 016, 120 Day Safety Update. As noted in the cover letter for Amendment 016 in order to prepare this safety update, data listings were revised for two ongoing studies. At this time we are providing the Case Report Forms and the revised data listings, which we consider to be raw data supporting the 120-Day Safety Update.

If you have any comments or questions concerning this submission, please do not hesitate to contact me at (609) 734-4403.

Sincerely yours,

Stephanie Rais

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

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

Takeda ORIGINAL ORIG AMENDMENT

TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.
101 CARNEGIE CENTER•SUITE 207
PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218

03 June, 1999
Ref: 060301SR

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

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 04 1999
HFD-510

Re: NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
120-Day Safety Report
NDA Amendment: # 016

Dear Dr. Sobel:

Pursuant to 21 CFR 314.50, we are hereby submitting our 120-Day Safety Update Report. By agreement (telephone call of March 19, 1999) with members of the Division, a three-week extension was granted for the filing of this report. The need for the extension was based on the Division's request that Takeda America Research and Development Corp. (TARDC) present ACTOS at the April 22 and 23, 1999 Metabolic and Endocrine Drugs Advisory Committee Meeting.

The 120-Day Safety Update is included in the attached 9 volumes.

Volumes 1 and 2 contain the revised ISS with the updated information. Volume 2 also contains updated information regarding the echocardiography report. The original echocardiography report was file on March 29, 1999 – amendment 005.

Volumes 3 through 9 contain the appendices and tables that support the data provided in Volumes 1 and 2. Volume 9 also contains the narratives of adverse events (i.e. deaths, serious adverse events and adverse events resulting in discontinuation).

In order to prepare this safety update, data listings were revised for two ongoing studies. These data listings will be filed as an Amendment to the NDA. Case Report Forms (CRFs) are available for the patients covered in this safety update and these will also be filed as an Amendment to the NDA. The data listings and CRFs will be filed the week of June 7, 1999.

If you have any comments or questions regarding this safety update, please do not hesitate to contact me at (609) 734-4403.

Sincerely yours,

Stephanie D. Rais

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

EDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

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

ORIG AMEN

21 May, 1999
Ref: 052101SR

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: # 015

Dear Dr. Sobel:

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

/S/ [redacted]
17-JUN

On March 2, 1999, we filed Amendment 001 containing stability data. As noted in the cover letter for Amendment 001, a commitment to provide stability data for three (3) commercial lots of each strength of tablets was included in the original NDA filed on January 15, 1999 – see NDA Section 4.A.3.8.1 (Volume 1.006, page 001). On March 2, we supplied 3-month stability data. At this time, we are providing the 6-month data for the accelerated storage condition.

The results are summarized in the attached Tables 1 through 3, see Attachment 1. Data is included in three reports from Takeda Chemical Industries, Ltd. as follows:

Report # A-35-1082	15 mg tablets	Attachment 2,
Report # A-35-1083	30 mg tablets	Attachment 3,
Report # A-35-1084	45 mg tablets	Attachment 4.

[redacted]

Attachment 1
Attachment 2
Attachment 3
Attachment 4

[redacted]

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

Sincerely,

Stephanie Rais

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

6/10/99

Attachment 1

Attachment 2

Attachment 3

Takeda

KEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

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

DUPLICATE

April 21, 1999
Ref: 042101SR

BM

DRUG AMENDMENT

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, MD 20857

RE: NDA 21-073
Pioglitazone HCL (AD-4833) Tablets
Amendment: 014

Dear Dr. Sobel:

Reference is made to telephone conversations that took place on April 7 between representatives of Takeda America Research & Development Center, Inc. and Dr. Misbin. Dr. Misbin requested case summaries for patients with selective cardiovascular effects.

On April 19, 1999, the information was faxed to Dr. Misbin. The purpose of this communication is to provide the information as a formal amendment to the pending New Drug Application.

If you have any questions or require any additional information, please do not hesitate to contact the undersigned or Dr. Roberta Schneider at (609) 452-1113.

Sincerely yours,

Stephanie D Rais

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

Takeda

KEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

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

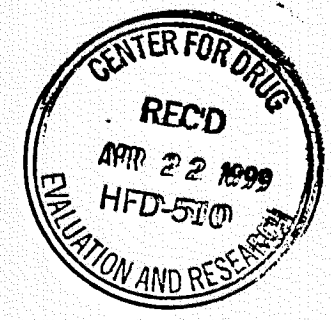
BP

DUPLICATE

April 20, 1999
Ref: 042001SR

NDA ORIG DEPARTMENT

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, MD 20857



RE: NDA 21-073
Pioglitazone HCL (AD-4833) Tablets
Amendment: 013

Dear Dr. Sobel:

Reference is made to telephone conversations that took place on various occasions between representatives of Takeda America Research & Development Center, Inc. and Dr. Herman Rhee. Dr. Rhee requested data tabulations including the lot numbers of drug used in the toxicology studies, dose levels with AUC data for various effects seen in animals, literature and other information on the effect of the glitazone class of drugs on PPAR gamma.

The information listed above has been provided to Dr. Rhee via three separate facsimile communications. The purpose of this submission is to provide the information (previously sent to Dr. Rhee) as a formal amendment to the pending New Drug Application. In addition to the data that was provided to Dr. Rhee, the fax cover pages are also included in this submission. The submission is organized by date of fax transmission.

If you have any questions or require any additional information, please do not hesitate to contact the undersigned at (609) 452-1113.

Sincerely yours,

Stephanie Rais

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

Takeda

KEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

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

April 13, 1999

ORIGINAL

BK1

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

Re: NDA 21-073
Pioglitazone HCl Tablets
Amendment 12

Dear Dr. Sobel:

Reference is made to your letter dated March 30, 1999 and received on April 5, 1999. Your letter, copy attached, states that we must request a waiver or file a plan for the assessment of pediatric safety and effectiveness.

In accordance with 21 CFR 314.55, we request a partial waiver of the pediatric study requirement.

ACTOS™ (pioglitazone HCL) is indicated for the treatment of Type 2 or noninsulin-dependent diabetes mellitus (NIDDM). Typically, Type 2 diabetes develops gradually in adults and usually after age 40. Thus, it was frequently referred to as adult-onset or maturity-onset diabetes.

Children usually develop Type 1 or insulin dependent diabetes mellitus and oral agents would not be effective in this setting. Previously, pediatric patients were not thought to develop Type 2 diabetes. However, several authorities in the field of endocrinology have indicated that there is a subpopulation of pediatric patients who metabolically resemble Type 2 diabetes patients and might benefit from oral antidiabetic therapy. In particular, obese adolescents (approximately 12 to 17 years of age) may develop diabetes associated with insulin resistance. Dr. Jaime Davidson presented information about this condition at the March 1998 Metabolic & Endocrine Advisory Committee Meeting.

Takeda America is considering clinical trials for this patient population and will file a clinical plan within 120 days of the receipt of your letter.

TDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

NDA 21-073
Amendment 12

Based upon the information presented above, we request that a waiver be granted under 21 CFR 314.55 c for pediatric patients up to approximately 12 years of age. Again, a clinical plan will be forwarded to cover pediatric patients approximately 12 to 17 years of age.

If you have any comments or questions concerning this amendment, please do not hesitated to contact Dr. Roberta Schneider or me at (609)452-1113.

Sincerely yours,

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

Enclosure: FDA Form 356h

CC: Dr. Diane Murphy
Assoc. Director for Pediatrics

TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

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

07 April, 1999
Ref.: 040701SR

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: # 010

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 third set of toxicology reports converted to electronic PDF files which are contained on the enclosed CR-ROM. The enclosed CD-ROM contains the acute and sub-chronic study reports, figures and summary tables. 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 third and final CD-ROM containing preclinical reports fulfills Dr. Rhee's request for electronic documents.

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. Herman Rhee **(DESK COPY, Letter Only)**
Ms. Jena Weber **(DESK COPY, Letter Only)**

ORIGINAL BC

TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

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

06 April, 1999
Ref: 040601SR

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: # 009

Dear Dr. Sobel:

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

At the request of Dr. Jim Wei (Biopharmaceutics Reviewer), the dissolution studies submitted in the original NDA (15 January, 1999; #000) were repeated in accordance with the Biopharmaceutics guideline on dissolution of immediate release dosage forms. Item 6 of the NDA was amended on March 31, 1999 (#007) with the new dissolution reports.

At this time, we are amending Item 4, Chemistry, Manufacturing and Controls with the repeated dissolution study reports for your review.

Furthermore, around mid-March, Ms. Jena Weber was informed that an FDA inspection had been scheduled for two Takeda Chemical Industry manufacturing facilities in Japan. One of the facilities was to undergo a PAI as a result of the review of a New Drug Application submitted by TAP (Takeda Abbott Pharmaceuticals). The facility scheduled for the PAI is also the facility that manufactures pioglitazone drug substance. Ms. Weber was contacted because we believed this was important information for the Division.

Unfortunately, the scheduled inspection has been postponed because it was to take place during the first week of May and that week is a National holiday in Japan. We believe the PAI will be rescheduled, but we do not know when it will take place.

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. Xavier Ysern, Chemistry Reviewer **(DESK COPY, Submission)**
Ms. Jena Weber, Project Manager **(DESK COPY, Letter Only)**