

Memorandum

June 30, 1999

JUN 30 1999

To: the NDA file 21-073 Actos (pioglitazone)

From: Solomon Sobel M.D., Director, Division of Metabolic and
Endocrine Drug Products

Subject: Approval of NDA

pioglitazone is the third member of this class to be considered for marketing. The others are troglitazone (Rezulin) and Rosiglitazone (Avandia) which have been approved. Pioglitazone was reviewed at a recent Advisory Committee in conjunction with rosiglitazone. Both safety and efficacy data for rosiglitazone were presented at that meeting but only safety data were presented in respect to pioglitazone. The reason for this was that pioglitazone had been submitted for review somewhat later than rosiglitazone and the efficacy evaluation had not been completed. However, it was decided to present both drugs because the safety considerations were considered paramount. Both rosiglitazone and pioglitazone were found to have less effect on the liver as judged by hepatic enzyme elevation as compared to troglitazone. In fact, there was no clearly demonstrable adverse effect on the liver by either drug.

Rosiglitazone was approved shortly after the Advisory Committee meeting with a recommendation for hepatic enzyme monitoring at the beginning of therapy and every 2 months for the first year and periodically thereafter.

We are now considering pioglitazone for marketing approval. The main issues are:

1. What is the safety profile of pioglitazone in respect to hepatic effects and what should be our degree of hepatic enzyme monitoring?
2. What effect does pioglitazone have in respect to serum lipid alterations?
3. What is the safety profile of pioglitazone in respect to cardiac effects?
4. What indications in respect to monotherapy and combined therapy have been established in the clinical trials?
5. Are there any problems in respect to pharmacotoxicology, chemistry, or pharmacokinetics?
6. Are there any comments from DDMAC in respect to the labeling?
7. What are we asking in respect to phase 4 commitments?

Discussion of above issues.

1. Pioglitazone was given to a total of 3650 patients. Of these, 0.33% had an elevation of ALT hepatic enzyme of greater than 3 times the upper limit of normal. (comparatively the incidence was 1.9% for troglitazone and 0.25% for rosiglitazone. For greater elevations (>8xULN) the incidences were 0.03%, 0.9% and 0.05% for pioglitazone, troglitazone, and rosiglitazone, respectively.

The Division had previously recommended for rosiglitazone that liver enzymes be measured at the initiation of therapy and then

monitored every 2 months for the first 12 months and then periodically thereafter.
We are making the identical recommendation for pioglitazone.

2. In the three monotherapy studies, there was a trend to a beneficial effect in respect to triglycerides (statistically significant), HDL cholesterol, and LDL cholesterol. In the study in which pioglitazone was combined with insulin the beneficial effect on triglyceride remained. Also, there was a slight increase in HDL. However there was a slight increase in LDL (non significant). In the study in which pioglitazone was combined with sulfonylurea the lipid effects were all in a favorable direction. In the study in which pioglitazone was combined with metformin, favorable effects were observed on triglycerides and HDL but the LDL was slightly elevated. All in all, the effects on lipids with pioglitazone are either favorable as seen in the monotherapy and of mixed effect in the combination studies with metformin and insulin.

3. The clinical studies did not give a signal for an adverse cardiac effect. A six-month placebo controlled echocardiographic study also did not show a deleterious effect. We have previously commented that a positively controlled echo study would have been a superior design. We will further address the possibility of adverse effects on the heart through phase 4 studies.

4. We have granted indications for use in patients with type 2 diabetes as monotherapy and also for use in combination with a sulfonylurea, metformin or insulin.

5. The Pharmacology reviewer recommended approval. We have discussed ongoing efforts through human hepatic tissue culture studies to help define the possible mode of toxicity of at least one member of the thiazolidinedione class of drugs. From a chemistry standpoint the application may be approved pending satisfactory results of the inspection of manufacturing facilities. From a pharmacokinetic standpoint there were requests for additional pharmacokinetic studies as outlined in the approval letter.

6. DDMAC has reviewed the labeling and we will incorporate their recommendations.

7. the phase 4 commitments will include additional pharmacokinetic studies and 2 clinical studies which are outlined in the approval letter.

Conclusions:

The Division recommends approval of pioglitazone.

The draft label of June 30, 1999 has been reviewed and it is found to be acceptable

-Solomon Sobel [redacted] 6/30/99

ADA-21-073

HFD-SID

ITFD-SID/Sobol/S Malozowski/R Misbin/XYSERW/S MOORE

HRhee/R STEIGERWALT/L PIAN/TSA/HROUT/J WEIX/HYAHN

ITFD-SII/SWEBER

APPEARS THIS WAY ON ORIGINAL

JUN 28 1999

Labeling T-con with Takeda
Thursday, June 24, 1999

Solomon Sobel, M.D.
Saul Malozowski, M.D.
Robert Misbin, M.D.
Todd Sahlroot, Ph.D.
Jena Weber, BS

Roberta Schnieder, M.D.
Annette Mathison, Ph.D.

The Division went through the package insert page by page (1-21) of the ACTOS labeling from May 28, 1999. Additions and deletions were specified.

These revisions that we requested should be completed by Monday, June 28, 1999. The company will send this updated version to us and provide a working copy on a disk. We need to insert the comments suggested by our Pharmacology team reviewers.

Phase 4 comments to Takeda from FDA:

- JW
1. 2 additional PK studies should be performed, including ketaconazole studies.
 2. 3 additional combination studies should be done including formal PK changes shown in males and females.
 3. Long-term observation of ACTOS utilizing liver function tests in 1000 patients for 3 years (this is in addition to what the company currently has).
 4. The cardiac problem (from Columbia University, class 2, 3, and 4):
 - Cardiac issue must be addressed in some way.
 - Patients with existing heart failure – ethical problems in enrolling this class of patients require a compelling need.
 - Possibility of using ~1000 patients, design an arm to use as a comparator in a managed healthcare system.

/SI


Jena Weber, RHPM

/SI


Robert Misbin, M.D.

APR - 2 1999

T-CON

Note to NDA file: 21-073

Takeda
Attention: Stephanie Rais
Wednesday, March 31, 1999 @ 2pm

Fax: 609-452-1218

Topic: 120-day Safety Update for NDA now under review, and efficacy content of the briefing document that will be submitted to the Agency and subsequently to the Advisory Committee.

Participants: <u>Takeda</u>	<u>FDA</u>
Stephanie Rais	Robert Misbin, M.D.
Roberta Schneider, M.D.	Jena Weber, RHPM

Company was informed that Dr. Misbin will not have his final draft completed for this application until June 1999, so a completed version will not be available by the time the AC convenes.

The format for the 120-day safety update is as follows: for study 11, old information from NDA will appear in regular type; the new information will appear in bold/italic type. Original and updated versions will be ready to compare/contrast. Dr. Misbin requested that a table of new patients that were not included in the original NDA be submitted.

Desk copies will follow, but will not include patient case report forms. These would be too numerous and would add up to extra volumes for our storage and review.

If any new cases of liver abnormalities or increase of CPK levels are reported, these should be highlighted for our attention.

The content of the briefing document for the Advisory Committee for monotherapy will include a presentation by Takeda on naive patients only. The document should arrive to us by April 6, 1999.

We will have a T-con with the company before the advisory meeting to discuss the topics that will be presented, agenda order and to make sure that we are all on the same page.

/s/ [Redacted]
[Signature]
Jena M. Weber, RHPM

/s/ [Redacted]
[Signature]
Robert Misbin, M.D.

Weber

NDA 21-073

MAR 30 1999

Takeda
Attention: Ms. Stephanie Rais
Regulatory Consultant
101 Carnegie Center, Suite 207
Princeton, NJ 08540

Dear Ms. Rais:

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: Actos™ (pioglitazone maleate) Tablets
Therapeutic Classification: Priority (P)
Date of Application: January 15, 1999
Date of Receipt: January 15, 1999
Our Reference Number: 21-073

This application was filed under section 505(b) of the Act on March 15, 1999, in accordance with 21 CFR 314.101(a). The user fee goal date will be July 15, 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.

Page 2

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.

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. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely,

/s/



3.30.99

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



TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

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

15 July, 1999
Ref: 071501SR

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: # 026

Dear Dr. Sobel:

The purpose of this Amendment is to provide Addendum 2 to our Phase IV study commitments. Phase IV commitments were provided to the Agency on July 6, 1999 (Amendment 019) and additional commitments were filed as Addendum 1 on July 7, 1999 (Amendment 022). During our meeting with representative of the Division and Dr. Jenkins on July 14, we were asked to provide additional details and a time line for completion of the studies. This information is contained herein.

We have agreed to the following studies as Phase 4 commitments.

Two pharmacokinetic studies:

- 1) An evaluation of the pharmacokinetic impact of concomitant administration of ketaconazole and ACTOS. This will be a 2-way crossover study utilizing a single dose ACTOS and a single dose of ketaconazole, and
- 2) An evaluation of the effect of administration of ACTOS on hepatic enzyme induction, This will be a steady state PK study with 2 weeks of ACTOS administration and single dose midazolam HCl.

Schedule: The protocols will be submitted to the FDA during the 3rd quarter of 1999 and the clinical conduct will begin no later than the 4th quarter of 1999. The final study reports will be provided to the agency by 3rd quarter of 2000.



Dr. Solomon Sobel

15 July, 1999

Page -2-

Three randomized, controlled clinical trials comparing the safety and efficacy of 6 months of treatment with ACTOS 30 mg versus ACTOS 45 mg in combination with:

- 1) sulfonylurea,
- 2) metformin, and
- 3) insulin.

Schedule: The protocols will be submitted to the FDA during the 3rd quarter of 1999, clinical conduct will begin no later than the 4th quarter of 1999. The final study report should be available to be filed to the agency within 18 to 24 months after study initiation.

Two additional studies with special clinical features:

- 1) a randomized, comparative clinical study in patients with type 2 diabetes mellitus and NYHA Class II and early Class III congestive heart failure. This will be an evaluation of efficacy and safety including hematologic and cardiac safety assessments, and.
- 2) a study evaluating the occurrence of serious liver disease in patients treated with ACTOS versus an appropriate control group.

Schedule: The designs for these two studies have not been finalized and will be discussed with the division prior to finalization of the protocols. The clinical phase of each study is anticipated to be somewhat protracted; study 1 will have a long recruitment period and study 2 will have a duration of treatment for 3 years. Therefore, we cannot provide study completion dates, however, we will pursue these studies with all due diligence.

If you have any questions concerning this submission, please do not hesitate to contact me at (609) 734-4404 or Ms. Stephanie Rais at (609) 734-4403.

Sincerely yours,



Roberta L. Schneider, M.D.
Vice President Drug Development



TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

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PRINCETON, NEW JERSEY 08540
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13 July, 1999
Ref: 071301SR

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, Maryland 20857

Re: NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment: # 025

Dear Dr. Sobel:

The purpose of this amendment is to provide official copies of information sent earlier today via facsimile to Dr. Wei, Biopharmaceutics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics. At the time this information was sent to Dr. Wei, a copy was also sent via facsimile to Ms. Jena Weber.

This amendment responds to telephone calls received yesterday from Dr. Wei and Dr. Ahn stating that the dissolution specification of [redacted] could not be accepted without supporting data. We had previously amended the NDA (see Amendment 18) with this specification. The Office of Clinical Pharmacology and Biopharmaceutics believes that the dissolution specification should be [redacted] unless data is submitted to show otherwise.

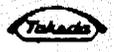
We are providing data to support our proposed dissolution specification of [redacted]. We were informed by Dr. Ahn that if data could be available by this morning, it would be reviewed and, if found acceptable, an addendum to the review package could be issued to allow the dissolution specification that we have proposed. (The attached data was faxed to Dr. Wei at 8:00 AM this morning.)

This official submission is also being sent via facsimile so that it is available to the Division today. The original signature copy will be sent via Federal Express, Priority Overnight Delivery to arrive tomorrow morning.

Please do not hesitate to contact me if you require any additional information. Furthermore, we will contact you on Wednesday regarding the outcome of this issue.

Sincerely yours,

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



[REDACTED]

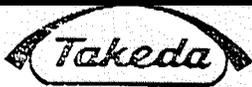
We are providing additional data in support of the dissolution specification of not less than [REDACTED] pioglitazone hydrochloride dissolved in [REDACTED] that was recently proposed in response to Dr. Wei's comments.

[REDACTED]

Tables 1 through 4, attached, provide profiles at 10, 20 and 30 minutes for lots in ongoing stability studies and for 3 of the commercial 45 mg batches recently produced for product launch.

[REDACTED]

000001



TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

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

July 8, 1999

Robert Misbin, M.D.
Food and Drug Administration
Division of Metabolic and Endocrine Drug Products
5600 Fishers Lane, HFD-510
Rockville, MD 20857-1706

Dear Dr. Misbin,

As we discussed, I am forwarding a copy of the narratives for the two patients who had bladder cancer identified during the ACTOS clinical program.

As I mentioned the ACTOS patient had been receiving ACTOS for 16 days when hematuria prompted a repeat urinalysis. At that time the patient revealed a history of bladder cancer treated 2 years earlier with regular follow-ups by the urologist. Additional information from the site, not included in the narrative, was that at the time of the repeat urinalysis, the patient indicated that her urologist had recently found a "spot" on her bladder that he was going to fix.

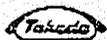
The other patient was in the metformin combination therapy study and had been receiving placebo for 51 days when, during an evaluation by a urologist for frequent urinary tract infections, he was noted to have bladder lesions requiring biopsy and fulgeration. The pathology report from the second surgery (not part of the narrative) indicated a high grade transitional cell lesion (carcinoma-in-situ).

Please call me if you need any additional information.

Sincerely,

Roberta L. Schneider, M.D.
Vice President, Drug Development

Enclosures





TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

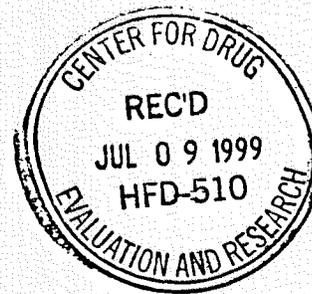
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July 7, 1999

NEW CORRERS

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 22

Dear Dr. Sobel:

This Amendment is an addendum to the Phase IV commitments filed to the Division in NDA Amendment 19. The additional Phase IV comments are listed below.

An enzyme induction study will be conducted. This will be a 2-way cross-over study in patients treated with pioglitazone HCl for 14 days and the administration of midazolam HCl (Versed®).

After discussions with representatives of the Division earlier today, we commit to a comparative clinical study in patients with type 2 diabetes mellitus and NYHA Class 2 and early Class 3 congestive heart failure. This study will evaluate efficacy and safety parameters focusing on hematologic and cardiac structure and function (echocardiographic or similar evaluation).

We trust these additional Phase IV commitments address all concerns discussed with representatives of the Division during today's teleconferences.

Sincerely,

Robert L. Schenck, M.D. V.P. Drug Development for
Mikihiko Obayashi, Ph.D.
President

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



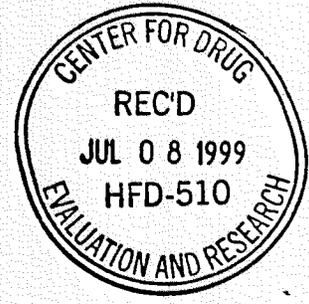
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July 7, 1999

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
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Document Control Room #14B-19
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Rockville, MD 20857

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



ORIGINAL
DL

Dear Dr. Sobel:

The purpose of this Amendment is to provide official responses to questions received from the Chemistry Reviewer, Dr. Ysern. On June 30, 1999, a facsimile communication was sent to us containing three requests to finalize the CMC section of the NDA. A copy of the fax is included in Attachment 1 of this submission.

Additionally, on July 1, teleconference took place between Dr. Ysern and Ms. Stephanie Rais, Regulatory Affairs Consultant for Takeda. During that telephone conversation, Dr. Ysern made some additional requests and these are listed in Attachment 1 following the Agency's June 30 facsimile.

At this time we wish to officially inform the Division that a specification has been set for particle size and a revised drug substance specification is provided in Attachment 2.

A request was made by Dr. Ysern that the description test in the drug product specifications be changed to clearly state how the different strengths will be distinguished. Additionally, concerning the drug product specifications, we have been asked by the Biopharmaceutics Reviewer to modify the dissolution specification. Agreement was reached on [redacted]. Both of these changes have been made to the drug product specifications and revised specifications are included in Attachment 3.

Regarding labeling, we accept the use of the ICH full storage statement. As of the writing of this letter, labels were printed at risk and contain the storage temperature included in the labeling in the NDA. It is our intention to discuss this matter further with Dr. Ysern and members of the Division. If we are allowed to use existing labels with the old statement, we will use the ICH statement for all future printings. If we are not allowed to use the printed materials, they will be destroyed and the reprinted labels will contain the revised storage statement.

Attachment 1

Attachment 2

Attachment 3

Dr. Sobel
Amendment 21, Page 2

The following issues were discussed between Dr. Ysern and Ms. Stephanie Rais on July 1, 1999.

Regarding the testing for related substances, the Agency did not make this a regulatory requirement; however, Dr. Ysern strongly recommended that the test be conducted. Testing for related substances will be done but not as a regulatory requirement.

Dr. Ysern noted that a drug substance retest date was not included in the NDA. He stated a retest date of one year seemed appropriate. Takeda Chemical Industries, Ltd. agrees to a one-year retest date.

We trust that this Amendment fully responds to all issues for Item 3 of the NDA. If there are any additional issues or, if clarification is needed for any items, please contact Ms. Rais at (609) 734-4403.

Sincerely yours,

Mikihiko Obayashi, Ph.D.
President