CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-073/S-002

Trade Name: Actos

Generic Name: (pioglitazone hydrochloride)

Sponsor: Takeda Pharmaceuticals America, Inc

Approval Date: February 25, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-073/S-002

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
Approvable Letter	
Labeling	
Medical Review(s)	
Chemistry Review(s)	X
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-073/S-002

APPROVAL LETTER

FEB 25 2000

NDA 21-073/S-002

Takeda Pharmaceuticals America, Inc.
Attention: Robert M. Pilson, R.Ph.
Manger, Regulatory Compliance
475 Half Day Road, Suite 500
Lincolnshire, IL 60069

Dear Mr. Pilson:

Please refer to your supplemental new drug application dated January 28, 2000, received January 31, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actos™ (pioglitazone hydrochloride) Tablets 15 mg, 30 mg and 45 mg.

This supplemental new drug application provides for the addition of the [redacted] facility in [redacted], as an [redacted] for Actos.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

Stephen K. Moore 2/24/00

Stephen K. Moore, Ph.D.
Chemistry Team Leader I, for
Division of Metabolic and Endocrine Drug Products,
(HFD-510)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 21-073
HFD-510/Div. Files
HFD-511/JWeber
HFD-510/XYsern/DGWu/SMoore
HFD-095/DDMS-IMT
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: jmw/February 14, 2000
Initialed by:XYsern 2/14/DGWu 2/14/EGalliers 2/18/00
final:2/23/00 2/23/00
filename: N21073.002

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-073/S-002

CHEMISTRY REVIEW(S)

FEB 14 2000

CHEMIST'S REVIEW

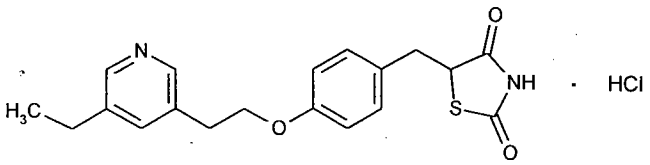
Organization CDER/HFD-510 Division of Metabolism and Endocrine Drug Products	**NDA # 21-073** Approved: 21-JUL-1999
Name and Address of Applicant: Takeda Pharmaceuticals America Inc. 101 Carnegie Center, Suite 207 Princeton, NJ 08540 Phone: (609) 452-1113 x-4409 Fax: (609) 452-1218	**Supplement** SCS-002 Doc. 28-JAN-2000 Rec. 31-JAN-2000 **Name Of The Drug** Actos™ Tablets **Nonproprietary Name** Pioglitazone Hydrochloride Tablets
Supplement provides for the addition of [redacted] facility, as an [redacted] facility for Actos™ Tablets.	**New Correspondence** --

Pharmacological Category: Hypoglycemic Agent, treatment of NIDDM.	**How Dispensed** Oral Rx	**Supporting Documents** --
Dosage Form Tablets	**Potencies** 15-, 30- and 45-mg	

Chemical Name and Structure

Pioglitazone

$C_{19}H_{20}N_2O_3S \cdot HCl$
MW = 356.43 + 36.57 = 392.90



(±)-5[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monohydrochloride

Comments: This Supplement –Changes Being Effected in 30 days- provides for an [redacted] **facility**. Currently, [redacted] is carried out at the approved site, [redacted] The [redacted] site is located on [redacted] A letter from [redacted] dated December 21 1999, stating that their facility is in compliance with cGMP, is adequately provided on page 1. The [redacted] facility has been found acceptable [based on profile] by the Office of Compliance (EER summary report dated 09-FEB-2000 attached). The [redacted] approved in NDA 21-073 are the methods utilized to perform [redacted] at [redacted] These methods have been transferred using an approved Transfer Protocol (certified by the applicant). The stability protocol with two minor revisions (pages 6 and 7) is adequately provided (pages 2 to 7). Accordingly to the "Guidance for the Industry, Changes to an Approved NDA or ANDA, November 1999" document (page 8), this information [redacted] could be send as a Supplement or in the Annual Report with proper identification of the change. *Adequate information has been provided.*

Conclusions and Recommendations Satisfactory CMC information has been provided to support [redacted] facility as an [redacted] site for the product, Actos™ (Pioglitazone HCl) Tablets. From the chemistry point of view, this supplement can be approved. Issue approval letter.

Reviewer Name (and signature) Xavier Ysern **Date Completed:** 10-FEB-2000

Xavier Ysern, PhD

R/D Init. Doug Sporn for S. Moore 2-14-00

filename: /nda/21073s02.doc

DISTRIBUTION: Original: NDA 21-073 cc: HFD-510 Division File/ JWeber / SMoore/ XYsern

CBE-30 days
AP

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21073/002**
Stamp: **31-JAN-2000** Regulatory Due: **31-JUL-2000**
Applicant: **TAKEDA AMERICA**
101 CARNEGIE CENTER STE 207
PRINCETON, NJ 08540

Priority: **1P** Org Code: **510**
Action Goal: District Goal: **26-JUN-2000**
Brand Name: **ACTOS (PIOGLITAZONE HCL)15/30/45MG TABS**
Established Name:
Generic Name: **PIOGLITAZONE HCL**
Dosage Form: **TAB (TABLET)**
Strength: **15-, 30- AND 45-MG**

FDA Contacts:			
J. WEBER	**(HFD-510)**	**301-827-6422**	**, Project Manager**
X. YSERN	**(HFD-510)**	**301-827-6420**	**, Review Chemist**
S. MOORE	**(HFD-510)**	**301-827-6430**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 09-FEB-2000 by S. FERGUSON (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **09-FEB-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-073/S-002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB 7 2000

NDA 21-073/S-002

Takeda Pharmaceuticals America, Inc.
475 Half Day Road
Suite 500
Lincolnshire, Illinois 60069

Attention: Robert M. Pilson
Manager, Regulatory Compliance

Dear Mr. Pilson:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ACTOS™ (pioglitazone hydrochloride) 15mg, 30mg, 45mg

NDA Number: 21-073

Supplement Number: S-002

Date of Supplement: January 28, 2000

Date of Receipt: January 31, 2000

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on March 31, 2000, in accordance with 21 CFR 314.101(a). All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 21-073/S-002
HFD-510/Div. Files
HFD-510/CSO/Weber

filename:

SUPPLEMENT ACKNOWLEDGEMENT

NDA 21-073 SUPPL. SCS-002

SUPPLEMENT SUBMITTED AS A *CHANGE BEING EFFECTED* (CBE)

Please determine whether this submission qualifies as a CBE by (date) 2-7-00.

All *required* primary reviewers:

Qualifies as CBE: (Signed) Lanie Isern 10-OCT-2000

Does not qualify: (Signed) _____

(If CMC, **Chemistry Team Leader** must also sign.)

Qualifies: Concurs for S. Mooll Does not qualify: _____

(If *in vivo* biopharmaceutics data are included, evaluation by **Biopharm reviewer** may be needed.)

Qualifies: _____ Does not qualify: _____

Return completed form to PM _____

(Name)

n:\dmedps1\egallier\form.cbe

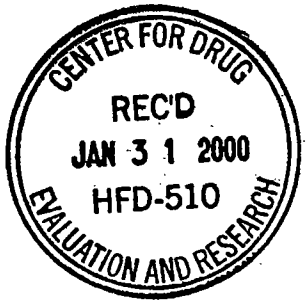
ORIGINAL

NDA NO. 21073 REF NO. 002

NDA SUPPL FOR SCS

475 Half Day Road • Suite 500
Lincolnshire, Illinois 60069
p/ 847.383.3000

TAKEDA PHARMACEUTICALS AMERICA, INC.



January 28, 2000

John Jenkins, M.D., F.C.C.P
Acting 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

Re: ACTOS™ (pioglitazone hydrochloride) 15mg, 30mg, 45mg
NDA No. 21-073
CHEMISTRY, MANUFACTURING AND CONTROLS
THIS SUPPLEMENT IS BEING FILED UNDER ———
"SUPPLEMENT--CHANGES BEING EFFECTED IN 30 DAYS"

Dear Dr. Jenkins:

This "Supplement--Changes Being Effected in 30 days", is being submitted to add ——— ———, as an ——— ——— to the above referenced New Drug Application. This supplement is based on 21CFR§314.70(g)(2), *Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change*; Guidance for Industry, Stability Testing of Drug Substances and Drug Products, Draft Guidance, June, 1998, p. 89; and Guidance for Industry — Postapproval Changes-- ——— ——— Currently, ——— is being performed by the site approved in the New Drug Application, ——— ———

In compliance with ———, Takeda Pharmaceuticals America, Inc. certifies that the ———, approved in NDA 21-073 have been transferred to ——— utilizing an approved Transfer Protocol. No postapproval commitments have been made by the applicant relating to the ——— has the capability to perform the intended ——— has certified (enclosed) that their facility is in compliance with current Good Manufacturing Practices.

TAKEDA PHARMACEUTICALS AMERICA, INC.

The documentation supporting the addition of [redacted] includes:

1. cGMP Certification by [redacted] signed by [redacted]
2. Stability Protocol with Revisions 1 and 2 (identical to the protocol approved in NDA 21-073) to be utilized for the [redacted] to be performed at [redacted] which provides a full description of the [redacted] be performed. The stability protocol has been assigned [redacted]
3. A statement indicating why a [redacted] CBE supplement is appropriate (i.e., the four circumstances above exist).
4. The name and address of the new [redacted]

Additionally, [redacted] will perform, on an as needed basis, [redacted] We feel that the documentation provided in this "Supplement--Changes Being Effected in 30 days" adequately supports the addition of [redacted] as a [redacted] for NDA 21-073. Please call me if you need further information regarding this submission.

This submission is also being provided concurrently to the Chicago District Office.

Sincerely,

Robert M Pilson

Robert M. Pilson, RPh
Manager, Regulatory Compliance
(847) 383-3023
(847) 383-3143 FAX

cc: Raymond Mlecko, District Director, Chicago District Office, 300 S. Riverside Plaza, Ste 550S, Chicago, IL 60606