CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-073/S008

Trade Name: Actos Tablets 15mg, 30mg, 45mg

Generic Name: (pioglitazone HCL)

Sponsor: Takeda Pharmaceuticals of North America, Inc

Approval Date: July 6, 2001

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APPLICATION NUMBER:

21-073/S008

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Microbiology Review(s)	
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Administrative/Correspondence Document(s)	X

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APPLICATION NUMBER:

21-073/S008

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-073/S-008

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

Dear Mr. Pilson:

Please refer to your supplemental new drug application dated January 25, 2001, received January 26, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actos® (pioglitazone HCl) Tablets, 15 mg, 30 mg, and 45 mg.

This supplemental new drug application provides for the elimination of multi-point dissolution profile testing as a component of the dissolution testing. The single-point dissolution testing that was approved in the original NDA application (Q [redacted] in 30 minutes), will remain part of the regulatory specifications.

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,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
7/6/01 01:46:01 PM

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APPLICATION NUMBER:

21-073/S008

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

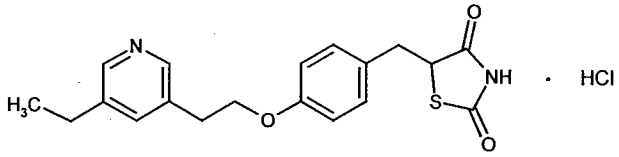
Organization CDER/HFD-510 Division of Metabolism and Endocrine Drug Products	**NDA # 21-073** Approved: 21-JUL-1999
Name and Address of Applicant: Takeda Pharmaceuticals America Inc. 101 Carnegie Center, Suite 207 Princeton, NJ 08540 Phone: (609) 452-1113 x-4409 Fax: (609) 452-1218	**Supplement** SCM-008 Doc. 25-JAN-2001 Rec. 26-JAN-2001 **Name Of The Drug** Actos™ Tablets **Nonproprietary Name** Pioglitazone Hydrochloride Tablets
Supplement provides for the elimination of multi-point dissolution profile testing as a component of the dissolution testing. Single-point dissolution testing, Q = [redacted] in 30 minutes, will remain part of the regulatory specifications	**Amendment(s)** --

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 –Requiring FDA Approval before the change is made- request the elimination of the multipoint dissolution profile testing as a component of the dissolution testing (release and stability). The supplement was sent for consult to the Biopharm Division. The Biopharm Division - see Dr. Steven Johnson review dated 02-JUL-2001 - does not have any objection to the elimination of the [unusual] continuous multipoint dissolution testing. As stated in Dr. Johnson review the use of multipoint dissolution testing is needed during development and situations were it is needed to prove equivalence. The single point dissolution testing, Q = [redacted] in 30 minutes, will remain part of the regulatory specifications.

Conclusions and Recommendations: The sponsor is allowed to eliminate multipoint dissolution profile testing. **For clarity, it should be communicated to the sponsor that the one point dissolution testing, Q = [redacted] in 30 minutes approved in the original submission and part of the regulatory specifications, remains unchanged.** From the chemistry point of view, this supplement can be approved. **Issue approval letter.**

Reviewer Name (and signature) **Date Completed:** 02-JUL-2001

Xavier Ysern, PhD

R/D Init.

filename: /nda/21073s08.doc

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

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/s/

Xavier Ysern
7/5/01 11:34:03 AM
CHEMIST

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Stephen Moore
7/17/01 12:30:42 PM
CHEMIST

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APPLICATION NUMBER:

21-073/S008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-073 SCM-008

BRAND NAME: Actos® **GENERIC NAME:** Pioglitazone hydrochloride

STRENGTH(S): 15 mg, 30 mg, and 45 mg tablets

SPONSOR: Takeda Pharmaceuticals North America, Inc
475 Half Day Road – Suite 500, Lincolnshire, IL 60069

SUBMISSION DATE: 25-JAN-2001 **REVIEW DATE:** 2-JUL-2001

CPB REVIEWER: Steven B. Johnson, Pharm.D.

CPB TEAM LEADER: Hae-Young Ahn, Ph.D.

SYNOPSIS

Takeda Pharmaceuticals North America has submitted a "Supplement requiring FDA approval before the change is made" for NDA 21-073 (Actos® - pioglitazone hydrochloride). The sponsor is requesting that dissolution profile testing be eliminated as a component of their release and stability specification. The dissolution method and tolerance specifications that the sponsor is using for Actos® is in accordance with those that were set in the original Clinical Pharmacology and Biopharmaceutics review for NDA 21-073 and are presented in Table 1.

Table 1. Dissolution Method and Tolerance Specifications – pioglitazone hydrochloride

Medium	Hydrochloric acid buffer
pH	2.0
Volume	900 mL
Apparatus	USP #2 (paddles)
Speed	50 RPM
Tolerance	NLT — (Q) @ 30 minutes

This request by the sponsor is unusual in that continuous multipoint dissolution testing was never asked of the sponsor by the Agency. The use of multipoint dissolution testing is usually only necessary during the development of a dissolution method, in lieu of certain bioequivalence testing as described in the "SUPAC IR Guidance for Industry," and in other situations in which it is necessary to compare dissolution profiles. However, continuous multipoint dissolution testing is not a routine component of dissolution testing and in this case was not requested by the Office of Clinical Pharmacology and Biopharmaceutics.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics recommends that the sponsor be allowed to eliminate dissolution profile testing as a component of dissolution testing for NDA 21-073 Actos® – pioglitazone hydrochloride) provided that this recommendation is not in conflict with the Chemistry recommendation.

Steven B. Johnson, B.S.Pharm, Pharm.D.
Division of Pharmaceutical Evaluation-II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader: 2-JUL-2001

FT initialed by Hae-Young Ahn, Ph.D., Team Leader: 3-JUL-2001

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/s/

Steve Johnson
7/20/01 09:19:45 AM
BIOPHARMACEUTICS

Hae-Young Ahn
8/8/01 09:44:44 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-073/S008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-073 SCM-008	Brand Name	ACTOS
OCPB Division (I, II, III)	DPE-2	Generic Name	Pioglitazone HCl
Medical Division	DMEDP (HFD-510)	Drug Class	Thiazolidinediones
OCPB Reviewer	Steven B. Johnson	Indication(s)	Type 2 DM
OCPB Team Leader	Hae-Young Ahn	Dosage Form	Tablet
Date of Submission	25-JAN-2001	Dosing Regimen	QD
Estimated Due Date of OCPB Review	3-JUL-2001	Route of Administration	PO
PDUFA Due Date	25-JUL-2001	Sponsor	Takeda Pharma North America
Division Due Date	6-JUL-2001	Priority Classification	NA

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				

Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X			**Proposed specification change**
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments		
	"X" if yes	**Comments**
Comments sent to firm ?	**X**	See Attachment
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-073, HFD-850(Lee), HFD-510(WeberJ), HFD-870(AhnH, Malinowoski, HuntJ), CDR

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/s/

Steve Johnson
7/20/01 09:18:06 AM
BIOPHARMACEUTICS

Hae-Young Ahn
8/8/01 09:42:32 AM
BIOPHARMACEUTICS