CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 021073

Trade Name: ACTOS TABLETS 15 MG, 30 MG, and 45 MG

Generic Name: PIOGLITAZONE HYDROCHLORIDE

Sponsor: TAKEDA ARMERICA RESEARCH AND DEVELOPMENT CENTER, INC.

Approval Date: 07/15/99

INDICATION(s): FOR THE IMPROVEMENT OF GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES MONOTHERAPY OR IN COMBINATION WITH SULFONYLUREAS, METFORMIN, OR INSULIN WHEN DIET AND THE SINGLE AGENT DOES NOT RESULT IN ADEQUATE GLYCEMIC CONTROL.

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Application Number: 021073

APPROVAL LETTER

NDA 21-073

Takeda America Research & Development Center, Inc.
Attention: Mikihiko Obayashi, Ph.D.
President
101 Carnegie Center, Suite 107
Princeton, New Jersey 08540

JUL 15 1999

Dear Dr. Obayashi:

Please refer to your new drug application (NDA) dated January 15, 1999, received January 15, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ACTOS™ (pioglitazone hydrochloride) Tablets 15, 30, and 45 mg.

We acknowledge receipt of your submissions dated March 2, 16, 23 (2), 29, and 31 (2), April 5, 6, 7, 13, 20, and 21, May 21, June 3, 11, and 30 (fax), and July 2 (fax), 5, 6 (fax), 7 (3 fax), 8 (fax), 9 (2 fax), 13 (2 fax), and 15, (5 fax), 1999.

This new drug application provides for the use of ACTOS™ (pioglitazone hydrochloride) Tablets for the improvement of glycemic control in patients with Type 2 diabetes as monotherapy or in combination with a sulfonylurea, metformin, or insulin when diet and the single agent does not result in adequate glycemic control.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft physician labeling submitted July 15, 1999, and the immediate container and carton labels submitted January 15, 1999. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-073." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submissions dated July 7 and 15, 1999:

1. To conduct an evaluation of the pharmacokinetic impact of concomitant administration of Actos and ketaconazole. This will be a 2-way crossover study utilizing a single dose of

Actos and a single dose of ketaconazole. The protocol will be submitted to the FDA by September 30, 1999; the clinical investigation will begin no later than December 31, 1999, and the final study report will be submitted to the FDA by September 30, 2000.

2. To conduct a 2-way, cross-over enzyme induction study in patients treated with pioglitazone HCl and Midazolam HCl. This will be a steady-state pharmacokinetic study with 2 weeks of Actos administration, and a single dose of midazolam HCl. The protocol will be submitted to the FDA by September 30, 1999; the clinical investigation will begin no later than December 31, 1999; and the final study report will be submitted to the FDA by September 30, 2000.

3. To conduct a 6-month study comparing the safety and efficacy of Actos 30 mg versus Actos 45 mg in combination with a sulfonylurea. The protocol will be submitted to the FDA by September 30, 1999; the clinical investigation will begin no later than December 31, 1999; and the final study report will be provided to the FDA within 24 months after study initiation.

4. To conduct a 6-month study comparing the safety and efficacy of Actos 30 mg versus Actos 45 mg in combination with metformin. The protocol will be submitted to the FDA by September 30, 1999; the clinical investigation will begin no later than December 31, 1999; and the final study report will be submitted to the FDA within 24 months after study initiation.

5. To conduct a 6-month study comparing the safety and efficacy of Actos 30 mg versus Actos 45 mg in combination with insulin. The protocol will be submitted to the FDA by September 30, 1999; the clinical investigation will begin no later than December 31, 1999; and the final study report will be submitted to the FDA within 24 months after study initiation.

6. To conduct a 3-year outcome study evaluating the occurrence of serious liver disease in 1000 patients treated with Actos compared to an appropriate control group. A draft protocol will be submitted to the Agency by October 31, 1999. The study will be initiated within three months of final protocol agreement, but not later than July 1, 2000.

7. To conduct a randomized, placebo-controlled 6-month clinical study in patients with type 2 diabetes and NYHA Class 2 and early Class 3 congestive heart failure. Evaluation of safety and efficacy parameters will focus on hematologic and cardiac structure and function (echocardiographic or similar evaluation). A draft protocol will be submitted to the Agency by October 31, 1999. The study will be initiated within three months of final protocol agreement, but not later than April 15, 2000.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments should be prominently labeled **"PHASE 4 COMMITMENTS."**

As you know, 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). We note that you have not fulfilled the requirements of 21 CFR 314.55. However, we acknowledge your letter dated April 13, 1999, requesting a waiver for patients younger than 12 years of age and stating your commitment to file a clinical plan within the next 120 days. The pediatric study requirement for the age range of 0 years to ≤ 11 years of age is waived. We are deferring submission of your pediatric studies for patients ≥ 12 years to 16 years of age until July 31, 2001. We acknowledge your commitment to submit your pediatric study plan for patients ≥ 12 years to ≤ 16 years of age within 120 days after approval of this application.

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 [NOTE: You should still submit a pediatric drug development plan] 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.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

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 contact Ms. Jena Weber, Regulatory Project Manager, at (301) 827-6422.

Sincerely,

/S/ [redacted] 7/15/99

John K. Jenkins, M[redacted]C.P.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL