CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-842

MEDICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: August 30, 2005

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-842
ActoplusMet (pioglitazone hydrochloride and metformin hydrochloride)
Treatment of type 2 diabetes

SUBJECT: NDA review issues and recommended action

Summary of issues

This is a fixed-dose combination drug product to be marketed in two strengths, containing pioglitazone 15 mg and either 500 mg or 850 mg of metformin. The product has not been specifically studied in clinical trials of glucose lowering. Rather the application is supported by the requisite bioavailability studies which demonstrate that the fixed combination products are bioequivalent for both the pioglitazone and metformin components to equivalent doses, respectively, of these drugs. Based on previous trials supporting combined use of pioglitazone and metformin for the control of glucose in DM2, this product is approved for 1) treatment to improve glycemic control as an adjunct to diet and exercise in patients already treated with a combination of pioglitazone and metformin, for 2) add-on therapy in patients not adequately controlled on metformin alone, and for 3) add-on therapy in patients who have initially responded to pioglitazone but who still require additional glucose lowering therapy.

There are no outstanding regulatory or scientific issues.

Recommendation

This application may be approved.

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/s/

David Orloff
8/29/2005 05:36:34 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #:	NDA 21842	APPLICATION TYPE:	NDA.....
SPONSOR:	Takeda	PROPRIETARY NAME:	ACTOPLUS MET.....
CATEGORY OF DRUG:	Antidiabetic	USAN / Established Name:	Pioglitazone/metformin.....
MEDICAL REVIEWER:	Robert I Misbin..	REVIEW DATE:	August 20, 2005.....

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
Oct 29, 2004			

ACTOPLUS MET tablets – 15 mg of pioglitazone with 500 mg and 850 mg of metformin

Recommendation: APPROVAL

Medical Officer – Robert I Misbin MD

NDA 21-842

This NDA is for a combination product that contains pioglitazone (PIO) plus metformin MET). Two strengths are to be marketed: 15 mg PIO plus 500 mg MET and 15 mg PIO plus 850 mg MET. By previous agreement with FDA, the basis of approval of this product will be demonstration of bioequivalence with PIO plus MET given as separate tablets. This information is presented in Table 1 of the proposed label.

The indications for the combination product are patients with type 2 diabetes who are already taking PIO plus MET and patients with type 2 diabetes who are inadequately controlled on MET alone and for whom addition of PIO is indicated. It has already been established by clinical trials that PIO is safe and effective when added to MET. No additional clinical trials are required. In addition, FDA has agreed to assume that splitting the dose of PIO does not change its effectiveness.

The labeling follows the approved labels for ACTOS and GLUCOPHAGE except that the ACTOPLUS MET tablets can be given once daily or twice daily (It is assumed that 15 mg PIO given twice daily will have the same safety/efficacy profile as 30 mg given once daily).

Pediatrics: The Sponsor has requested a deferral of pediatric trials. I believe a waiver is more appropriate. I see no reason to perform clinical trials with this product on pediatric patients.

Recent Change in Metformin Label: DMEDP has requested the change in all metformin-containing products that ***congestive heart failure (CHF)*** no longer be a contraindication. This request is based on results of two observational studies that found that patients with CHF treated with metformin appeared to have an improved prognosis. CHF need not be included as a contraindication in the ACTOPLUS MET label.

The following financial disclosure information has been submitted:

1 Form OMB No. 0910-0396. The applicant certifies that Takeda has not entered into any financial arrangement with the clinical investigators named in the lists included in the NDA whereby the value of compensation to the investigator could be affected by the outcome of the study. It was signed 10/13/04 by John Yates, President, Takeda Global Research

2 The applicant further certifies that none of the listed clinical investigators disclosed a proprietary interest in the product or an equity interest in Takeda.

3 The applicant certifies that no listed investigator was the recipient of other payments such as honoraria, consultation fees, research grants, or compensation in the form of equipment from Takeda .

Recommendation: APPROVAL

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/s/

Robert Misbin
8/22/2005 02:43:18 PM
MEDICAL OFFICER

routine approval

David Orloff
8/22/2005 05:06:32 PM
MEDICAL OFFICER