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APPLICATION NUMBER:

22-024

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-024	Submission Date: 3/31/06
Brand Name	ACTOPLUS MET XR
Generic Name	Pioglitazone Hydrochloride and Metformin Hydrochloride Extended Release Tablets
Reviewer	Jayabharathi Vaidyanathan, Ph.D.
Team Leader (Acting)	Jim Wei, Ph.D.
OCP Division	DCP-2
OND Division	Division of Metabolic and Endocrine Products
Sponsor	Takeda
Submission Type	505 (b) (2)
Formulation; Strength(s)	15 mg/ 1000 mg and 30 mg/ 1000 mg ; Oral tablets
Indication	Treatment of Type 2 Diabetes Mellitus

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I Executive Summary

Takeda has developed a fixed-dose combination tablet formulated as 15 mg/1000 mg and 30 mg/1000 mg strengths from the following active ingredients from approved compounds Actos (pioglitazone HCl) NDA 21-073 held by Takeda Pharmaceuticals and Fortamet (metformin HCl extended release) NDA 21-574 held by Andrx Labs respectively.

The efficacy and safety of the concomitant use of pioglitazone and metformin has previously been evaluated in controlled clinical trials (NDA 21-073). Concomitant administration of the separate commercial pioglitazone and metformin tablets in adult patients with type 2 diabetes was approved by the FDA in 1999 as a part of the original marketing approval of pioglitazone.

Pioglitazone is approved for once-daily administration at doses of 15, 30 and 45 mg. Metformin extended release (Fortamet) is available in 500, and 1000 mg tablets and is approved for individualized treatment up to a maximum daily dose of 2500 mg in adults depending on effectiveness and tolerability. To improve gastrointestinal tolerability, it is recommended that Fortamet be administered with an evening meal. Fortamet has been shown to be bioequivalent to immediate release metformin under these dosing conditions. Pioglitazone can be administered regardless of meals.

To aid in the approval of this application the sponsor has submitted 2 bioequivalence studies and 1 food effect study. There were no clinical studies done with the to-be marketed combination product and the pharmacokinetic studies were designed to bridge the proposed combination tablets to the clinical safety and efficacy database supporting the use of pioglitazone in combination with metformin existing under the approved NDA.

A Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2) has reviewed the information provided in the NDA 22-024 for ACTOPLUS MET XR tablets and finds it acceptable. Recommendations and labeling comments should be sent to the sponsor as appropriate.

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Jaya Vaidyanathan, Ph.D.
OCP/DCP-2

A clinical pharmacology briefing was held for NDA 22-024 on December 18, 2006; the attendees were Dr. Chandra Sahajwalla, Dr. Suresh Doddapaneni, Dr. Emmanuel Fadiran, Dr. Jim Wei, Dr. Robert Misbin, Dr. Jayabharathi Vaidyanathan and Carol Noory.

B Phase 4 Commitments

None.

C Summary of CPB Findings

The summary of results from the clinical pharmacology studies is provided below.

Bioequivalence:

Bioequivalence studies were conducted for the two strengths of combination tablet. Results indicate that the pioglitazone and metformin from ACTOPLUS MET XR 15 mg/1000 mg and 30 mg/1000 mg tablets were bioequivalent to Actos and Fortamet commercial tablets given concomitantly under fed conditions. The conclusions are based on the findings that the 90% CI for the ratio of geometric means (test/reference) for AUC and C_{max} were within the 80-125% interval.

Food effect:

The results demonstrated that after administration of the highest strength combination tablet (30 mg/1000 mg) under fed conditions, the AUC of pioglitazone was similar as compared to the fasted state while there was a decrease in Cmax by approximately 18%. While the metformin AUCinf and Cmax increased by 85% and 98% respectively in presence of food. Since metformin is indicated to be administered with food, ACTOPLUS MET XR is also recommended to be administered with food.

II QBR

A General Attributes

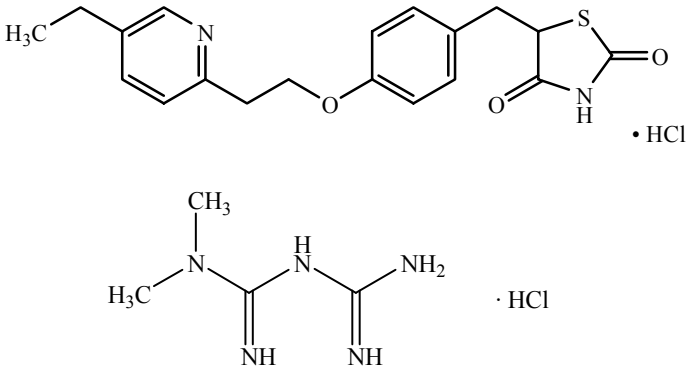
What are the highlights of the chemistry and physico-chemical properties of ACTOPLUS MET XR?

ACTOPLUS MET XR contains 2 oral antihyperglycemic drugs used in type 2 diabetes; pioglitazone hydrochloride and metformin hydrochloride. Pioglitazone ([(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride) (Figure 1) belongs to thiazolidinedione class. The molecule contains one asymmetric center, and the synthetic compound is a racemate. The two enantiomers of pioglitazone interconvert *in vivo*. Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of $C_{19}H_{20}N_2O_3S$•HCl and a molecular weight of 392.90.

Metformin hydrochloride (N, N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other class of oral antihyperglycemic

agents. It is a white crystalline powder with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.62.

Figure 1: Chemical structure of pioglitazone (top) and metformin (bottom).



What is the proposed mechanism (s) of action and therapeutic indication?

ACTOPLUS MET XR combines two antihyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes: pioglitazone hydrochloride, a member of thiazolidinedione class, and metformin, a member of the biguanide class. This is a 505 (b) (2) application. The proposed indication for the combination tablet is the same as that for the individual drugs.

Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

Metformin improves glucose tolerance in patients with type 2 diabetes, reducing both basal and postprandial plasma glucose levels. Metformin also decreases hepatic glucose production, decreases intestinal absorption of glucose and improves sensitivity by increasing peripheral glucose uptake and utilization.

The proposed indication for ACTOPLUS MET XR is as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of pioglitazone and metformin or whose diabetes is not adequately controlled with metformin alone, or for those patients who have initially responded to pioglitazone alone and require additional glycemic control.

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