

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-024

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS

M E M O R A N D U M

DATE: October 26, 2008

TO: ACTOPLUS MET XR (pioglitazone HCl plus metformin HCl extended release)
(NDA 22-024)

FROM: Mary H. Parks, M.D., Director, Division of Metabolism and Endocrinology
Products (DMEP)
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SUBJECT: REMS requirement for ACTOPLUS MET XR

This memorandum documents the basis for our decision to require a Risk Evaluation and Mitigation Strategy (REMS) for the ACTOPLUS MET XR NDA.

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
- (F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for ACTOPLUS MET XR to ensure that the benefits of the drug outweigh the risks of heart failure associated with the use of pioglitazone-containing products, based on clinical trial data. In reaching this determination, we considered the following:

- A. Approximately 24 million people in the U.S. have diabetes, of whom more than one-third will require more than one anti-diabetic agent to maintain adequate glycemic control within several years of initiation of drug therapy. The potential market for ACTOPLUS MET XR is several million patients annually.
- B. Patients with type 2 diabetes who require more than one anti-diabetic agent for glycemic control are at risk for a variety of complications including heart disease, stroke, blindness, kidney failure, nervous system damage, amputations, and death if untreated. ACTOPLUS MET XR is an option for those individuals who are inadequately treated with anti-diabetic monotherapy.
- C. The expected benefit of this combination drug product in terms of glycemic control is greater than either component administered as monotherapy.
- D. The expected duration of therapy is over a patient's lifetime.
- E. One of the drugs comprising ACTOPLUS MET XR, metformin, has been associated with various other adverse effects, including lactic acidosis. Additionally, in a long-term cardiovascular outcomes trial, 5238 patients were randomized to pioglitazone (n=2605) or placebo (n=2633) in addition to their background anti-diabetic medications. The percentage of patients who had a serious heart failure event was higher for patients treated with pioglitazone (5.7%, n=149) than for patients treated with placebo (4.1%, n=108). In patients treated with an insulin-containing regimen at baseline, the incidence of serious heart failure was 6.3% (n=54/864) with pioglitazone and 5.2% (n=47/896) with placebo. For those patients treated with a sulfonylurea-containing regimen at baseline, the incidence of serious heart failure was 5.8% (n=94/1624) with pioglitazone and 4.4% (n=71/1626) with placebo.
- F. ACTOPLUS MET XR contains metformin and pioglitazone and is not a new molecular entity.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that ACTOPLUS MET poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use ACTOPLUS MET. FDA has determined that ACTOPLUS MET is a product that has serious risk (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decisions to use, or continue to use ACTOPLUS MET.

The elements of the REMS will be Medication Guide and a timetable for submission of assessments of the REMS.

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/s/

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