

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-224**

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



11/4/08

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

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**MEMORANDUM**

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**DATE:** October 17, 2008

**TO:** File, Trilipix (fenofibrate) (NDA 22-224)

**FROM:** Mary H. Parks, M.D., Director, Division of Metabolism and Endocrinology Products (DMEP)  
Amy G. Egan, M.D., M.P.H., Deputy Director for Safety, DMEP

**SUBJECT:** Proposed Risk Evaluation and Mitigation Strategy (REMS) for Trilipix (fenofibrate)

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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 to ensure that the benefits of Trilipix (fenofibrate) outweigh its risk of rhabdomyolysis when Trilipix is co-administered with a statin. In contrast to other fibrates, none of which are approved for co-administration with a statin, Trilipix (fenofibrate) is indicated for co-administration with a statin.

In reaching this determination, we considered the following:

- A. In 2007, the number of retail prescriptions written for a fibric acid derivative was \_\_\_\_\_  
\_\_\_\_\_ the estimated number of patients prescribed a fibric acid derivative in 2007 was \_\_\_\_\_  
Of these patients \_\_\_\_\_

\_\_\_\_\_ The potential market under the proposed combination therapy indication, mixed dyslipidemia and CHD or a CHD risk equivalent, is \_\_\_\_\_ patients.

- B. Patients with mixed dyslipidemia are at increased risk for CHD. Trilipix (fenofibrate) will be used in conjunction with a statin to reduce triglyceride levels and raise HDL-C levels in patients with mixed dyslipidemia and CHD or CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.
- C. The benefit of Trilipix (fenofibrate) over and above statin monotherapy in patients with mixed dyslipidemia is expected based on Trilipix-induced improvements in TG and HDL-C levels and the results of some post-hoc analyses of cardiovascular outcomes trials in which fibrate-treated patients with baseline abnormalities in TG and HDL-C dyslipidemia had reductions in cardiovascular morbidity.
- D. The expected duration of therapy is over a patient's lifetime.
- E. Trilipix (fenofibrate) has been associated with various other adverse effects that involve the hepatobiliary system (e.g., transaminitis, cholelithiasis, and pancreatitis) and the renal and urinary system (e.g., increased serum creatinine). Based on the proposed new indication for this drug product of co-administration with a statin, a literature review was conducted. Epidemiological studies suggest an increased occurrence of a serious risk, rhabdomyolysis, associated with the combination use of a statin and a fenofibrate over the respective monotherapies. This safety information shows that:
- The incidence rate for hospitalized rhabdomyolysis for patients treated with atorvastatin + a fenofibrate was 22.45 per 10,000 person-years (CI: 0.57-125), while the incidence rate for monotherapy with atorvastatin was 0.54 per 10,000 person-years (CI: 0.22-1.12) and the incidence rate for monotherapy with fenofibrate was 0 (CI: 0-14.58).
  - Rhabdomyolysis is a serious adverse event and no incremental benefit of Trilipix (fenofibrate) on cardiovascular morbidity and mortality over and above that demonstrated for statin monotherapy has been established.
- F. Trilipix (fenofibrate) is not a new molecular entity (NME), but this product will be a new approval.

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 Trilipix (fenofibrate) poses a serious and significant public health concern requiring distribution of a Medication Guide. FDA has determined that Trilipix (fenofibrate) is a product that has a serious risk of which patients should be made aware because information concerning this risk could affect patients' decisions to use Trilipix (fenofibrate). FDA has also determined that Trilipix (fenofibrate) is a product for which patient labeling could help prevent serious adverse events.

b(4)

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

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/s/

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Amy Egan  
11/4/2008 03:18:05 PM  
MEDICAL OFFICER

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