Heart Failure Warning Strengthened for TZDs

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The labels of all thiazolidinediones now carry a black box warning about the risk of heart failure, the Food and Drug Administration announced on Aug. 14.

The strengthened warning emphasizes that thiazolidinediones (TZDs) may "cause or exacerbate congestive heart failure in some patients," according to the FDA.

The agency sent the manufacturers letters requesting the labeling change in May. Product labeling for the TZDs rosiglitazone (Avandia), manufactured by GlaxoSmithKline, and pioglitazone (Actos), manufactured by Takeda, previously contained information about heart failure (HF) in the warnings and precautions sections, but the labeling is being strengthened following recent revelations about rosiglitazone's cardiovascular safety.

The FDA says that the concern over heart failure is "separate" from the concerns over the increased MI risk associated with rosiglitazone, which was the subject of a joint meeting of the FDA's Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee in July.

The committees concluded then that data from meta-analyses of the rosiglitazone clinical program show an increased risk for myocardial ischemia for the type 2 diabetes therapy. The agency is currently reviewing similar pooled data from the pioglitazone clinical program.

"This new boxed warning addresses FDA's concerns that despite the warnings and information already listed in the drug labels, these drugs are still being prescribed to patients without careful monitoring for signs of heart failure," Dr. Steven Galson, director of the FDA's Center for Drug Evaluation and Research, said in a statement.

"The strengthened warning advises health care professionals to observe patients carefully for the signs and symptoms of heart failure, including excessive, rapid weight gain, shortness of breath, and edema after starting drug therapy," according to the FDA.

The updated labeling states that initiation of rosiglitazone or pioglitazone is contraindicated in patients with New York Heart Association class III or IV heart failure. After treatment with these products is initiated or if the dose is increased, patients should be observed for signs of heart failure. If a patient is diagnosed with heart failure, discontinuation or dose reduction of the TZD "should be considered."

The rosiglitazone data cited by the FDA include a year-long echocardiographic study in type 2 diabetic patients with NYHA class I or II heart failure, who were receiving treatment for diabetes and HF; the study did not find treatment-related differences in the change from baseline in ejection fraction. But the risk of heart failure exacerbations was higher in patients on rosiglitazone (6%), compared with those on placebo (4%). In addition, the rates of worsening edema, worsening dyspnea, and increases in heart failure medications were higher among those on rosiglitazone (25%, 26%, and 33%, respectively), compared with those on placebo (9%, 17%, and 18%).

Among the pioglitazone data cited by the FDA was a 24-week study comparing the TZD to glyburide in 518 patients with NYHA class II and III heart failure and an ejection fraction below 40%. In the study, overnight hospitalizations for heart failure were reported in nearly 10% of those on pioglitazone, compared with almost 5% of those on glyburide, an adverse event that was "more marked" in patients taking insulin at baseline and in those older than age 64.

The label revision also extends to the combination products that include the TZDs: Avandaryl (rosiglitazone and glimepiride), Avandamet (rosiglitazone and metformin), and Duetact (pioglitazone and glimepiride).

The FDA is continuing to monitor postmarketing reports of heart failure; its review of rosiglitazone and the possible increased risk of MI also is ongoing. ■

For more information, go to: www.fda.gov/medwatch/safety/2007/safety07.htm#rosi_pio. Adverse or serious events associated with TZDs should be reported to the FDA's MedWatch program at www.fda.gov/medwatch.

Brian Marson, assistant news editor for Elsevier's "The Pink Sheet," contributed to this report.