Summary - FDA
April 2002

Products: ACTOS [pioglitazone HCl]; AVANDIA [rosiglitazone maleate]

Audience: Primary care providers, endocrinologists, cardiologists and other healthcare professionals treating patients with type 2 diabetes mellitus

What's Changed: Modification to the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the labels for ACTOS and AVANDIA

Physicians and patients with diabetes are alerted to the possibility of fluid retention when either drug is used as monotherapy or in combination with insulin. The fluid retention may lead to, or exacerbate, congestive heart failure [from WARNINGS/cardiac failure/ACTOS and AVANDIA].

In post-marketing experience with either product, cases of CHF have been reported. [from PRECAUTIONS/general/ACTOS; from ADVERSE REACTIONS/AVANDIA]]

What is the Scientific Evidence Supporting this Change [from current professional labels]:

In one 16-week U.S. double-blind, placebo-controlled clinical trial involving 566 patients with type 2 diabetes, ACTOS at doses of 15 mg and 30 mg in combination with insulin were compared to insulin therapy alone. This trial included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions as follows: arterial hypertension (57.2%), peripheral neuropathy (22.6%), coronary heart disease (19.6%), retinopathy (13.1%), myocardial infarction (8.8%), vascular disease (6.4%), angina pectoris (4.4%), stroke and/or transient ischemic attack (4.1%), and congestive heart failure (2.3%). In this study two of the 191 patients receiving 15 mg ACTOS plus insulin (1.1%) and two of the 188 patients receiving 30 mg ACTOS plus insulin (1.1%) developed congestive heart failure compared with none of the 187 patients on insulin therapy alone. All four of these patients had previous histories of cardiovascular conditions including coronary artery disease, previous CABG procedures, and myocardial infarction. Analysis of data from this study did not identify specific factors that predict increased risk of congestive heart failure on combination therapy with insulin. [from WARNINGS/cardiac failure/ACTOS].

In two 26-week U.S. trials involving 611 patients with type 2 diabetes, *Avandia* plus insulin therapy was compared with insulin therapy alone. These trials included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions, including peripheral neuropathy (34%), retinopathy (19%), ischemic heart disease (14%), vascular disease (9%), and congestive heart failure (2.5%). In these clinical studies an increased incidence of cardiac failure and other cardiovascular adverse events were seen in patients on *Avandia* and insulin combination therapy compared to insulin and placebo.

Patients who experienced heart failure were on average older, had a longer duration of diabetes, and were mostly on the higher 8 mg daily dose of *Avandia*. In this population, however, it was not possible to determine specific risk factors that could be used to identify all patients at risk of heart failure on combination therapy. Three of 10 patients who developed cardiac failure on combination therapy during the double blind part of the studies had no known prior evidence of congestive heart

failure, or pre-existing cardiac condition. The use of Avandia (rosiglitazone maleate) in combination therapy with insulin is not indicated. [from WARNINGS/Cardiac failure/AVANDIA]

What Action Should be Considered [from current professional labels]:

Patients should be observed for signs and symptoms of heart failure. [from WARNINGS/cardiac failure/ACTOS and AVANDIA].

Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure should immediately report these symptoms to their physician. [from PRECAUTIONS/information for patients/ACTOS and AVANDIA].

The drug should be discontinued if any deterioration in cardiac status occurs. [from WARNINGS/cardiac failure/ACTOS and AVANDIA].

Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during clinical trials; therefore, ACTOS and AVANDIA are not recommended in these patients. [from WARNINGS/cardiac failure/ACTOS and AVANDIA].