

## Indiana Medicaid Therapeutics Committee Therapeutic Class Review Summary

### **Therapeutic Class:**

Hypoglycemics, Insulin-Response Enhancers (Thiazolidinediones)

### **Overview:**

Thiazolidinediones (also known as thio-glitazones, glitazones, or TZDs) were first introduced to the US market in January 1997. Troglitazone (Rezulin<sup>®</sup>) was the first medication approved by the Food and Drug Administration (FDA) in this category. This medication was termed a novel oral hypoglycemic and became known as an “insulin sensitizer.” Thiazolidinediones specifically targeted insulin resistance and offered a new approach to the treatment of type 2 diabetes. In December 1997, troglitazone was suspended from marketing in the UK due to concerns with drug-induced hepatotoxicity. In June 1998, the National Institutes of Health terminated a study investigating troglitazone’s potential for preventing type 2 diabetes due to one documented case of fatal hepatotoxicity. In 1999, two new thiazolidinediones, pioglitazone and rosiglitazone, were approved by the FDA for the treatment of type 2 diabetes. With newer and apparently safer agents available, troglitazone’s indication was changed for use in type 2 diabetes unresponsive to other therapies. The FDA and the manufacturer withdrew troglitazone from the US market in March 2000. To date, the incidence of hepatotoxicity appears to be minor with both pioglitazone and rosiglitazone. However, liver enzyme monitoring is recommended prior to the initiation of therapy and periodically thereafter. In addition, the risk of fracture should be considered when prescribing either of these agents for female patients, since an increased incidence of fractures has been observed in female patients receiving either pioglitazone or rosiglitazone for the treatment of diabetes.

Thiazolidinediones are agonists for the peroxisome proliferator-activated receptor (PPAR) gamma, which regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. Thiazolidinediones improve insulin sensitivity and beneficially modify other components of the metabolic syndrome, such as dyslipidemia, vascular procoagulant state, and blood pressure. Placebo-controlled trials have demonstrated that thiazolidinediones generally lower HgbA<sub>1c</sub> as effectively as sulfonylureas and metformin.

Pioglitazone and rosiglitazone are approved for the treatment of type 2 diabetes as monotherapy and in combination with other oral hypoglycemic agents, ie, metformin, sulfonylureas, and insulin. Avandamet<sup>™</sup> (rosiglitazone and metformin), Actoplus Met<sup>™</sup> (pioglitazone and metformin) and Avandaryl<sup>™</sup> (rosiglitazone and glimepiride) are discussed in the antidiabetic agent therapeutic class review. Pioglitazone and rosiglitazone are equivalent in efficacy and tolerability. While not indicated for the treatment of dyslipidemia, in most studies, pioglitazone and rosiglitazone have been shown to raise HDL-cholesterol and lower triglycerides. A less pronounced beneficial effect on triglycerides and HDL-cholesterol and a greater increase in LDL-cholesterol may be seen with rosiglitazone compared to pioglitazone. With regard to LDL-cholesterol, however, an increased floatation rate occurs, indicating a shift in LDL density from small-density LDL to less atherogenic large buoyant particles. No significant drug interactions have been reported with either agent to date, although pioglitazone is metabolized partially by

cytochrome P450 3A4. The adverse effects of pioglitazone and rosiglitazone that occur with greater frequency than in patients treated with placebo are fluid retention and edema.

The prescribing information for both pioglitazone and rosiglitazone indicates that the drugs should not be used by individuals with New York Heart Association (NYHA) Class III and IV heart failure as thiazolidinediones can cause fluid retention, which may exacerbate or lead to heart failure. Researchers of a retrospective review published in the September 2003 issue of *Mayo Clinic Proceedings* concluded that thiazolidinediones should be avoided in patients with left ventricular function or chronic renal insufficiency based on records from six men who developed signs and symptoms of congestive heart failure (CHF) and pulmonary edema after 1 to 16 months of therapy. Four of the patients had a history of chronic renal insufficiency, 1 had ischemic cardiomyopathy, and 1 had no known predisposing factors for congestive heart failure or pulmonary edema. The American Heart Association and the American Diabetes Association issued a consensus statement in December 2003 that addressed the monitoring of patients on thiazolidinediones for fluid retention and CHF. In particular, the authors reminded prescribers that edema is more common when thiazolidinediones are used in combination with insulin. Also, the authors recommended that prescribers start with low doses of thiazolidinediones with very gradual dose escalations in patients with multiple CHF risk factors, asymptomatic abnormal ventricular function, or class I or II CHF.

Thiazolidinediones are effective in the treatment of type 2 diabetes and may have beneficial effects on cardiovascular risk factors associated with insulin resistance. Proper patient selection and monitoring is encouraged. Long-term efficacy and safety should be demonstrated in outcome trials.

<b>Generic Name</b>	<b>Brand Name</b>	<b>Dose</b>	<b>Manufacturer</b>
Pioglitazone	Actos <sup>®</sup>	15-45 mg QD	Takeda
Rosiglitazone	Avandia <sup>®</sup>	4-8 mg/day given QD or BID	GlaxoSmithKline

**Summary:**

Pioglitazone and rosiglitazone are equivalent in efficacy and tolerability. To date, the incidence of hepatotoxicity, which led to the withdrawal of troglitazone from the US market, appears to be unremarkable for both drugs. Selection of an agent for the preferred drug list should be based upon the total cost impact to the program.