Therapeutic Class:
Hypoglycemics, Insulin-Response Enhancers (Thiazolidinediones)

Overview:
Thiazolidinediones (also known as thioglizones, glitazones, or TZDs) were first introduced to the U.S. market in January of 1997. Troglitazone (Rezulin® – Parke Davis) was the first medication approved by the Food and Drug Administration 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 Parke-Davis withdrew troglitazone from the U.S. market in March 2000. To date, the incidence of hepatotoxicity appears to be minor with both pioglitazone and rosiglitazone.

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. Placebo-controlled trials have demonstrated that thiazolidinediones generally lower HgbA1c as effectively as sulfonylureas and metformin. 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 status since 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 conclude 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 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.

Pioglitazone and rosiglitazone are approved for the treatment of type 2 diabetes as monotherapy and in combination with other oral hypoglycemic agents, i.e., metformin, sulfonylureas and insulin. Avandamer™ (combination product consisting of rosiglitazone and metformin) is discussed in the antidiabetic agent therapeutic class review.

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<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Dose</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td>Pioglitazone</td>
<td>Actos®</td>
<td>15-45 mg QD</td>
<td>Takeda</td>
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<tr>
<td>Rosiglitazone</td>
<td>Avandia®</td>
<td>4-8 mg/day given QD or BID</td>
<td>GlaxoSmithKline</td>
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References from Therapeutic Class Review: