

Criteria for Use of the Thiazolidinediones, Rosiglitazone and Pioglitazone

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

These criteria were developed using the best evidence currently available. The following recommendations are dynamic and will be revised, as new clinical data become available. These guidelines are not intended to interfere with clinical judgment. Rather, they are intended to assist practitioners in providing consistent, high quality care that is cost effective.

Indications for VA Patients

Rosiglitazone and pioglitazone should be reserved for selected patients due to their modest effect on reducing HbA1c compared to sulfonylureas or metformin, unproven long-term cardiac safety profile, and high cost.

Monotherapy

Rosiglitazone and pioglitazone should not be used as monotherapy since there is no advantage in reducing HbA1c over sulfonylureas (SU) or metformin. Data on these agents as monotherapy indicates an average absolute decrease in HbA1c of 0.2-0.7% from baseline. Therefore, a TZD should generally not be used as monotherapy, until evidence is available showing superiority to sulfonylureas or metformin on clinical outcomes.

Combination therapy

Rosiglitazone or pioglitazone as part of a combination regimen with SU, metformin, or insulin should be made available as outlined below.

Rosiglitazone or pioglitazone + sulfonylurea (SU)	Rosiglitazone or pioglitazone + Metformin	Rosiglitazone or pioglitazone + Insulin ¹
<p>Inadequate glycemic control with SU monotherapy</p> <p style="text-align: center;">AND</p> <p>Had an inadequate response or have a contraindication to combining a SU with metformin</p> <p><i>Treatment options</i></p> <ul style="list-style-type: none"> • When desired decrease in HbA1c is < 2%, consider an alpha-glucosidase inhibitor, bedtime insulin, or a TZD • When desired decrease in HbA1c is ≥ 2%, use insulin 	<p>Inadequate glycemic control with metformin monotherapy</p> <p style="text-align: center;">AND</p> <p>Had an inadequate response or have a contraindication to combining metformin with a SU or a meglitinide</p> <p><i>Treatment options</i></p> <ul style="list-style-type: none"> • When desired decrease in HbA1c is < 2%, consider an alpha-glucosidase inhibitor, bedtime insulin, or a TZD • When desired decrease in HbA1c is ≥ 2%, use insulin 	<p>Insulin in doses > 50 units/day ²</p> <p style="text-align: center;">AND</p> <p>HbA1c > 8% or exceeds target HbA1c value by > 1% as based on VHA guidelines</p> <p style="text-align: center;">AND</p> <p>Had an inadequate response with combination insulin and metformin or have a contraindication to metformin</p>
<p>The average absolute decrease in HbA1c when combining a TZD with a SU is 0.5-1.2%</p>	<p>The average absolute decrease in HbA1c when combining a TZD with metformin is 0.6-0.8%</p>	<p>The average absolute decrease in HbA1c when combining a TZD with insulin is 0.4-1.3%</p>

1. May be considered in selected patients requiring high doses of insulin (e.g., > 100), as a means of decreasing insulin requirements; should be done under a specialist's care (Buse 1998)
2. This is an arbitrarily chosen value based on the insulin dose used in the clinical trials. The average dose in the clinical trials was 75 units with wide standard deviations ranging from 30-45 units. The 50-unit value represents the dose at the lower end of the standard deviation. VISNs can establish their own threshold of insulin dosage above which TZD is clearly indicated. Appropriateness of TZD should be made based upon a clinical evaluation of the individual patient.

Dosages and Administration

- May be given without regard to meals.
- No dosage adjustment required for renal insufficiency. There are insufficient data at this time to recommend use in end stage renal disease.
- The current sulfonylurea and/or metformin dose should be continued when adding rosiglitazone or pioglitazone. The dose of the sulfonylurea may need to be reduced if the patient reports hypoglycemia.
- May continue current insulin dose; however, if plasma glucose levels decrease to less than 100-120 mg/dL, the dose of insulin should be decreased by 10-25%. Continue to monitor the patient for further adjustments.

Rosiglitazone

When added to a sulfonylurea or metformin, the usual starting dose of rosiglitazone is 4mg once daily or 2mg twice daily. Maximum daily dose is 8mg once daily or 4mg twice daily.

When added to insulin, rosiglitazone should be dosed at 4mg daily. Doses greater than 4mg are not currently approved.

Pioglitazone

Pioglitazone may be initiated at 15-30mg administered once daily when combining with sulfonylurea, metformin, or insulin. Maximum daily dose is 45mg.

Warnings/Adverse Events

Phase II and III trials have shown that rosiglitazone and pioglitazone do not cause hepatotoxicity any more than placebo. In post-marketing experience with these agents, hepatitis and elevation of liver enzymes ≥ 3 times the upper limit of normal has been reported; however, causality has not been established. Nevertheless monitoring for liver function tests (LFTs) is recommended. (See Monitoring Parameters)

Use of TZDs whether alone or in combination with other oral agents or insulin can cause fluid retention resulting in peripheral edema, development of or exacerbation of heart failure, and abnormalities in hematological parameters such as hemoglobin and hematocrit. The risk appears to be greatest when combining rosiglitazone or pioglitazone with insulin.

Patients with New York Heart Association (NYHA) Class 3 and 4 cardiac status have not been included in the clinical trials. Until safety data is available, the use of rosiglitazone or pioglitazone is not recommended for these patients. Very few patients with NYHA Class 1 and 2 have been included in the clinical trials; therefore, careful assessment of the risk versus benefit of TZD therapy in this population should be performed, especially if used with insulin. If a TZD is prescribed, close monitoring of the patients' fluid status is necessary. Initial dose should begin with the lowest approved dose. Any increases in dose should be made gradually after several months of treatment and close monitoring of fluid status.

Dose dependent increase in weight of 1-4 kg can occur with these agents. When combined with insulin, increases of 4-5 kg can occur. Waist-to-hip ratios were unchanged.

Increases in low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and total cholesterol have been observed with the TZDs. Preliminary data suggest that the increase in LDL-C is predominantly due to the larger buoyant particles of LDL, which may be less atherogenic than the small, dense LDL. The LDL/HDL ratio is preserved, although with rosiglitazone, there is a lag time of several months before HDL-C rises relative to LDL-C. Triglycerides decrease with pioglitazone, whereas the effect with rosiglitazone is variable.

Rosiglitazone and pioglitazone may induce ovulation in premenopausal anovulatory patients and/or in those with Polycystic Ovarian Syndrome. Need for contraception should be discussed with the patient as appropriate.

Monitoring Parameters

HbA1c should be monitored at 4 and 6 months with significant improvement defined as reaching goal or a $\geq 1\%$ reduction. Therapy should be discontinued if goals are not met.

Liver monitoring

- Liver function tests (LFTs) and bilirubin should be checked prior to the initiation of a TZD, then periodically thereafter.
- Do not initiate if patient has evidence of liver disease or an ALT > 2.5 x the upper limit of normal. Do not use if patient experienced jaundice while taking troglitazone
- Patients with mildly elevated values (ALT 1-2.5 x upper limit normal) at baseline or anytime during therapy should be evaluated to determine the cause of liver enzyme elevation. Initiation or continuation of therapy with the TZD in patients with mildly elevated values should proceed with caution and include appropriate follow-up
- If ALT $> 2.5 - \leq 3$ x upper limit of normal, LFTs should be evaluated more frequently until the levels return to normal or pretreatment values. If ALT > 3 x the upper limit of normal, while taking a TZD, recheck another level as soon as possible. If ALT remains > 3 x the upper limit, discontinue use.
- Monitor for signs and symptoms suggestive of hepatic dysfunction including nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine and jaundice. Patients should be instructed to inform their physician should these symptoms develop.

Cardiac monitoring

Observe patients for signs and symptoms of heart failure.

Rosiglitazone or pioglitazone should be discontinued if deterioration in cardiac status occurs.