Criteria for Non-formulary 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.

1. 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, unknown 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 decease 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 [1,2]**
Inadequate glycemic control with SU monotherapy ***AND*** Had an inadequate response or have a contraindication to combining a SU with metformin *Treatment options* • 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	Inadequate glycemic control with metformin monotherapy ***AND*** Had an inadequate response or have a contraindication to combining metformin with a SU or a meglitinide *Treatment options* • 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	Insulin in doses > 50 units/day [3] ***AND*** HbA1c > 8% **or** exceeds target HbA1c value by > 1% as based on VHA guidelines ***AND*** Had an inadequate response with combination insulin and metformin or have a contraindication to metformin
The average absolute decrease in HbA1c when combining a TZD with a SU is 0.5-1.2%	The average absolute decrease in HbA1c when combining a TZD with metformin is 0.6-0.8%	The average absolute decrease in HbA1c when combining a TZD with insulin is 0.4-1.3%

[1] Rosiglitazone received an approvable letter in February 2001 for combination with insulin. However, at present, this combination is not indicated. Both rosiglitazone and pioglitazone have similar risk for edema and can lead to heart failure. See Warnings/Adverse Events

[2] 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)

[3] 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.

2. Dosages and Administration

- May be given without regard to meals.
- No dosage adjustment required for renal insufficiency. There is 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. At present, there are insufficient data on the use of triple oral therapy that includes a TZD. In general, patients unable to achieve glycemic goal with combination sulfonylurea and metformin therapy often require the addition of insulin to meet treatment goals.

Rosiglitazone
4-8mg/day given once daily or divided into 2 doses

Pioglitazone
15-30mg administered once daily when combining with sulfonylurea, metformin, or insulin.

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.

3. 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 $\geq$ 3 times the upper limit of normal has been reported; however, causality has not been established.

Plasma volume has been shown to increase with these agents, causing edema and abnormalities in hematological parameters such as hemoglobin and hematocrit. Patients with New York Heart Association (NYHA) Class III and IV Congestive heart failure (CHF)/angina 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 I and II CHF 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.

In clinical trials and post-marketing data, combining rosiglitazone or pioglitazone with insulin resulted in the development of peripheral edema in approximately 15% of patients. Ten patients developed heart failure on rosiglitazone + insulin, 3 of whom had no known prior evidence of CHF or pre-existing cardiac failure. In a clinical trial comparing pioglitazone + insulin versus insulin alone, four patients receiving the combination developed congestive heart failure compared to none receiving insulin alone.

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.

4. Monitoring Parameters

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

Liver monitoring

- Do not initiate if patient has evidence of liver disease or an ALT > 2.5 x the upper limit of normal.
- Liver function tests (LFTs) and bilirubin should be checked every 2 months for the first year, then periodically thereafter. The frequency of LFT monitoring after the first year has not been defined. While there are few reports of LFT abnormalities, the FDA has not yet withdrawn these stringent monitoring recommendations.
- If ALT > 3 x the upper limit of normal, recheck another level as soon as possible. If ALT remains > 3x 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.

References

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