Pioglitazone Criteria for Use

VA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

Pioglitazone is the thiazolidinedione (TZD) agent of choice. Access to and distribution of rosiglitazone has been restricted as part of a Risk Evaluation and Mitigation Strategy (REMS) program, referred to as the Avandia-Rosiglitazone Medicines Access Program, which limits the use of rosiglitazone to:

- Patients already being successfully treated with rosiglitazone
- Patients whose blood sugar cannot be controlled with other antidiabetic medicines and who, after consulting with their provider, do not wish to use pioglitazone.

Healthcare providers and patients must be enrolled in the Avandia-Rosiglitazone Medicines Access Program in order to prescribe and receive rosiglitazone. After *November 18, 2011*, rosiglitazone will no longer be available through retail pharmacies. Patients who are enrolled in the Avandia-Rosiglitazone Medicines Access Program will receive their medicine by mail order through specially certified pharmacies participating in the program.

Exclusions (if ONE is selected, patient is not eligible)

- ❑ Type 1 Diabetes Mellitus
- ❑ Pre-diabetes: impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)
- ❑ New York Heart Association (NYHA) Class III or IV heart failure†
- ❑ Developed significant heart failure while taking another thiazolidinedione (TZD)
- ❑ Experienced jaundice while taking another TZD and no alternate etiology could be found
- ❑ Active bladder cancer or prior history of bladder cancer

†Use with caution in patients with NYHA Class I/II heart failure or patients with risk factors for heart failure. Pioglitazone is not recommended in symptomatic heart failure

Inclusions

Monotherapy (*BOTH of the following must be fulfilled in order to meet criteria)*

- ❑ Is intolerant of or has contraindications to both sulfonylureas and metformin
- ❑ Target value for HbA1c based on VA/DoD Guidelines is likely to be attainable based on clinical trial data

In the pivotal trials the AVERAGE decrease in HbA1c ranged from 0.6-0.8%. The mean decrease was greater in those with higher baseline HbA1c (e.g.; 2.5% in those with baseline HbA1c of 10%)

Combination (2 drug) oral therapy *(ALL 3 of the following must be fulfilled in order to meet criteria)*

- ❑ Inadequate glycemic control on monotherapy with metformin (at maximally tolerated dose) or sulfonylurea (at ≥ 50% maximal dose or highest tolerated dose)
- ❑ Unable to tolerate or has contraindications to addition of a 2nd agent from the above mentioned group
- ❑ Target value for HbA1c based on VA/DoD Guidelines is likely to be attainable based on clinical trial data

In the pivotal clinical trials the AVERAGE decrease in Hba1c ranged from 0.8 -1.7% for the combination of a SU +TZD and 0.6-1.0% for metformin + TZD

Triple oral therapy *(ALL 3 of the following must be fulfilled in order to meet criteria)*

- ❑ Inadequate glycemic control on 2-drug therapy with a sulfonylurea (at ≥ 50% maximal dose or highest tolerated dose) and metformin (at highest tolerated dose) [2]
- ❑ Patient is not a good candidate for or refuses addition of insulin
- ❑ Target value for HbA1c based on VA/DoD Guidelines is likely to be attainable based on clinical trial data

In the triple oral therapy trials, the AVERAGE decrease in HbA1c ranged from 0.4 – 1.9%

Combination with insulin *(ONE must be selected in order to meet criteria)*

- ❑ Evidence of insulin resistance (e.g. acanthosis nigricans, polycystic ovary disease, total insulin dose > 1 unit/kg/day or > 100 units/day - these doses are considered as guidance and are not intended as absolute) and not at target HbA1c goal.¶
- ❑ Inadequate glycemic control with insulin therapy (e.g. due to hypoglycemia, patient refusing intensification of insulin regimen)

¶Consider use of metformin prior to a TZD unless contraindicated

In the clinical trials, where a TZD was added to insulin, the AVERAGE decrease in HbA1 was 1.2% (30mg dose) and 1.5% (45mg dose).

Dosage and Administration

- Recommended starting dose is 15-30mg once daily (for patients with NYHA Class I or II heart failure, the starting dose is 15mg once daily. The dose may be taken without regards to meals
- Maximum dose 45mg daily. The maximum daily dose is 15mg if pioglitazone is concomitantly administered with gemfibrozil or other strong CYP2C8 inhibitors
- If hypoglycemia occurs when an insulin secretagogue or insulin is co-administered with pioglitazone, the dose of the insulin secretagogue or insulin should be reduced. For insulin, it is recommended that the dose be reduced by 10-25% with further adjustments based on glycemic response.

Issues for Consideration

See Table 1

Renewal Criteria

A significant minority of patients does not have a response to TZDs; therefore, to continue use, meaningful improvement in glycemic control after 3-6 months of therapy in the absence of significant adverse events must be demonstrated.

In the case of pioglitazone + insulin in patients with significant insulin resistance, a meaningful decrease in insulin dose and/or improvement in glycemic control must be demonstrated.

[1]Insulin may be considered at any time prior to using a TZD; however, it should be considered if patient is symptomatic or a greater reduction beyond what is achievable by TZDs is desired.

[2]To determine patient specific A1C goals, refer to the VA/DoD Clinical Practice Guidelines for Management of Diabetes http://www.oqp.med.va.gov/cpg/DM_base.htm

[3]If patient is near their glycemic goal (e.g. <0.5% from goal), consider increasing sulfonylurea to the maximum approved daily dose

Table 1: Issues for Consideration

	Warnings/Adverse Events	Monitoring
Edema/ Cardiac Failure	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 TZDs with insulin	Careful assessment of the risk versus benefit of TZD therapy must be performed in patients with NYHA Class I or II heart failure, patients with risk factors for heart failure, and patients with depressed ejection fraction. Close monitoring of fluid status is necessary. Monitor patients for signs and symptoms of heart failure. If heart failure develops, manage according to current standards of care and consider discontinuing or reducing dose. Patients should be instructed to report weight gain, edema or shortness of breath particularly if the onset is acute or the amount progresses rapidly.
Weight gain	Dose dependent increase in weight of 1-5.4 kg (median values) can occur with these agents. The greatest median increase in weight was seen when used in combination with insulin.	Patients should be instructed to inform their provider if significant weight gain (e.g. > 3kg) develops within first few months of TZD use or after an increase in dose.
Hepatic Effects	Phase II and III trials have shown that TZDs do not cause hepatotoxicity any more than placebo. In post-marketing experience with these agents, hepatic failure or abnormal liver tests have been reported; however, causality has not been established.	Liver function tests (LFTs) and bilirubin should be checked prior to the initiation of pioglitazone. In patients with abnormal liver test, initiate pioglitazone with caution. Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than 3 times the upper limit of the reference range), treatment should be interrupted and investigation done to establish the probable cause. Do not restart

		pioglitazone if liver injury is confirmed and no alternate etiology can be found. Patients who have serum ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative etiologies are at risk for severe drug-induced liver injury, and should not be restarted on pioglitazone. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with pioglitazone can be used with caution.
Lipid changes	Increases in low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and total cholesterol have been observed with the TZDs. 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. Triglycerides decrease with pioglitazone.	Assess and maintain cholesterol levels according to current standards of care
Ovulation	TZDs 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.
Fractures	TZDs have been associated with an increased risk of upper and lower limb bone fractures in female patients. These sites of fractures differ from hip or spine fractures that are typically associated with post-menopausal osteoporosis.	Assess and maintain bone health according to current standards of care
Macular Edema	There have been rare post-marketing reports of new onset or worsening macular edema with the TZDs, which have been described as decreased visual acuity or blurred vision or were diagnosed on routine ophthalmologic exam. Concurrent peripheral edema was frequently reported. In some cases, discontinuation of the TZD or dosage reduction resulted in resolution of the macular edema.	Patients should have an eye exam at least annually by an ophthalmologist. Patients reporting any kind of visual symptoms should be promptly referred to an ophthalmologist
Bladder Cancer	5-year interim data from an ongoing 10-year observational cohort study found that a statistically significant association between any pioglitazone exposure and increased bladder cancer risk was not observed (HR= 1.2, 95% CI: 0.9-1.5). However, results from this study suggested that taking pioglitazone > 12 months was associated with an increase in risk (HR 1.4 [95% CI 0.9 – 2.1]) which reached statistical significance after > 24 months of use (HR 1.4 [95% CI 1.03 – 2.0]). A French retrospective cohort study also suggests increased risk of bladder cancer with pioglitazone which has led to the suspension of its use in France.	Instruct patients to contact their healthcare provider if they experience any sign of blood in the urine or a red color in the urine or other symptoms such as new or worsening urinary urgency or pain on urination since starting pioglitazone, as these may be due to bladder cancer