

**Regence BlueCross BlueShield of Oregon • Regence BlueShield
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Medication Policy Manual

Policy No: dru131

Topic: Actos[®], pioglitazone – containing medications (Actos, ACTOplus Met[®], Duetact[™])

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IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Pioglitazone (Actos[®]), a thiazolidinedione, is an oral medication used alone or in combination with metformin, a sulfonylurea, or insulin for the treatment of type 2 diabetes. Pioglitazone/metformin (ACTOplus Met[®]) and pioglitazone/glimepiride (Duetact[™]) are oral combination products used for the treatment of type 2 diabetes.

Policy/Criteria

- I. Most contracts require prior authorization approval of pioglitazone prior to coverage. Pioglitazone may be considered medically necessary when at least one of the following criteria A, B or C below is met.

- A. **Type 2 Diabetes:** Initial authorization for pioglitazone may be considered medically necessary for patients with type 2 diabetes meeting the following criteria under 1 and 2:

- 1. There is documentation that the patient's A1C value is over 7%.

AND

- 2. Treatment with metformin is contraindicated, not tolerated, or has been inadequate in reducing A1C to goal of 7% or less after 90 days of therapy.

OR

- B. **Nonalcoholic Steatohepatitis:** Initial authorization for pioglitazone may be considered medically necessary for patients with nonalcoholic steatohepatitis when metformin was ineffective, contraindicated, or not tolerated.

OR

- C. **Polycystic Ovary Syndrome:** Initial authorization for pioglitazone may be considered medically necessary for patients with polycystic ovary syndrome when metformin was ineffective, contraindicated, or not tolerated.

II. Administration and Authorization Period

- A. Regence considers pioglitazone to be a self-administered medication.
 - B. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

- III.** Pioglitazone is considered investigational when used for all other conditions, including, but not limited to:
- A.** Advanced melanoma
 - B.** Alzheimer's disease
 - C.** Atopic dermatitis
 - D.** Crohn's disease
 - E.** Gliomas
 - F.** HIV-related lipodystrophy
 - G.** Metabolic syndrome
 - H.** Pre-diabetes
 - I.** Type 1 diabetes

Position Statement

Background

- The American Diabetes Association has established a treatment algorithm for type 2 diabetes. ^[28, 69]
 - * The recommended therapy for newly diagnosed type 2 diabetes includes using metformin in addition to lifestyle interventions.
 - * Metformin can lower A1c by about 1.8% compared to placebo and is associated with reducing complications of diabetes.
 - * If a goal A1C of $\leq 7\%$ is not achieved, then the addition of either basal insulin, a sulfonylurea, or a thiazolidinedione is recommended, depending on individual patient considerations.
 - * If the goal A1C is then not reached, the addition of a medication from one of the other classes is recommended.

- * Ultimately, the use of intensive insulin + metformin ± a thiazolidinedione is recommended, if needed, to achieve the goal A1C level.

Goal of Treatment

- The American Diabetes Association has set an A1C treatment goal for patients with diabetes to not exceed 7%. [28]
 - * Lowering A1C to below or around 7% has been shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes. [28]
 - * Recent large-scale, randomized controlled trials have failed to find a significant long-term benefit of intensive glycemic control (A1C goals less than 6.5%) for lowering cardiovascular (macrovascular) risk. [28, 70-72]
 - * Intensive glycemic control (A1C goals less than 6.5%) may increase mortality in some patients. [70]
- The American Association of Clinical Endocrinologists (AACE) treatment guidelines suggest an A1C treatment target for patients with diabetes of 6.5%. However, this recommendation was last updated in 2007 prior to the availability of the most recent diabetes treatment outcomes trials that raise concerns about aggressive A1C lowering. [10]

Thiazolidinedione Overview

- Pioglitazone and rosiglitazone can lower A1C by up to 1.6 percentage points compared to placebo over 6 months. [11-12]
- Thiazolidinedione therapy has demonstrated a clinical benefit in reduction of A1C as monotherapy compared to placebo and as adjunctive therapy. [3, 5-6, 9, 11-16, 22-27, 34-36]
- Clinical trials have not demonstrated a superior benefit of thiazolidinediones over first line therapies such as metformin. [1-9, 15-16, 73]
- Thiazolidinedione therapy generally results in similar glycemic control when compared with sulfonylureas. Thiazolidinedione therapy generally results in lowered insulin resistance whereas sulfonylureas generally result in lower serum cholesterol, compared with each other. [37-40]
- When compared head-to-head, pioglitazone and rosiglitazone demonstrated similar effects on reduction in A1C in type 2 diabetic patients. [15]
- The value of pioglitazone in the treatment of "metabolic syndrome" is unclear since there are

many other options with established benefit in treating the individual components associated with this syndrome.

Clinical Efficacy

I. Type 2 Diabetes

- A large-scale, reliable trial (PROactive) with pioglitazone failed to achieve its primary endpoint of reducing the total mortality and macrovascular morbidity in type 2 diabetic patients. ^[17-18]
 - * The composite endpoint was made up of death, non-fatal myocardial infarction (MI), silent MI, stroke, major leg amputation, acute coronary syndrome, coronary revascularization, and leg revascularization.
 - * Statistical significance was only demonstrated when several secondary endpoints were combined.
 - * Caution is urged when using pioglitazone in patients with a history of a previous MI.
- A published subgroup analysis suggests that patients with a history of MI, pioglitazone may reduce the risk of another MI (53 patients needed to be treated to prevent one additional MI). However, patients were more likely to have worsening heart failure that required hospitalization (only 43 patients needed to be treated to result in one additional serious case of heart failure). ^[58]

II. Other Uses

A. NONALCOHOLIC STEATOHEPATITIS

- Metformin, pioglitazone, and rosiglitazone have been evaluated in small, preliminary trials to evaluate their usefulness in the management of nonalcoholic steatohepatitis (NASH).
- In an open-label, randomized, placebo-controlled fashion, **metformin** 850 mg twice daily + calorie restricted diet was evaluated against calorie-restricted diet alone in 36 patients with laboratory-confirmed NASH. At the end of 6 months, patients receiving metformin had significant improvements in serum AST, insulin, C-peptide and insulin-resistance. ^[42]

- **Rosiglitazone** has been evaluated in non-controlled and controlled studies in adult patients with biopsy-confirmed NASH. In studies lasting up to 1 year, patients treated with rosiglitazone had statistically significant improvements in transaminase levels, and histological features, though no long-term benefits were noted. Though these were small studies, they all generally point to an overall improvement in clinical status in patients with NASH. ^[43-45]
- **Pioglitazone** has been evaluated in randomized, placebo-controlled, single-blind, and double-blind trials in adult patients with biopsy proven NASH. Significant improvements were noted in ALT, GGT, hepatocellular injury and fibrosis. ^[30, 73] Though these studies were small (less than 100 patients per trial), these findings are consistent with previous studies. ^[46, 47]

B. POLYCYSTIC OVARY SYNDROME (PCOS)

- The initial treatment of PCOS should involve lifestyle modification with an emphasis on controlled eating patterns, regular aerobic exercise and management of blood pressure and lipid abnormalities. ^[48,49]
- Metformin should be considered as an initial intervention in most women with PCOS, especially in those women who are overweight or obese. Metformin improves many metabolic abnormalities in PCOS and may improve menstrual cyclicity and the potential for pregnancy. ^[48,49]
- Pioglitazone and rosiglitazone have been studied in small, preliminary trials to evaluate their usefulness in the management of PCOS. ^[19-21, 50-55]
 - * In aggregate, these trials have generally shown that the thiazolidinediones improve insulin resistance, hyperglycemia and glucose intolerance related to PCOS.
 - * Major deficiencies in these trials, including lack of ITT analyses, lack of blinding, lack of control groups and small study size, make the validity and usefulness of these trials uncertain.
 - * Nevertheless, there appears to be a consensus that thiazolidinedione therapy may be useful in patients who either do not respond to, or cannot tolerate, metformin. ^[48,49]

C. INVESTIGATIONAL USES

- * **Advanced melanoma** – a phase II randomized, open-label, active controlled trial

in 76 patients with advance melanoma suggested that pioglitazone +_rofecoxib added to trofosfamide may have a modest effect on progression free survival. Larger, well designed trials are needed to establish safety and efficacy. ^[64]

- * **Atopic dermatitis** – a published retrospective case series suggests that rosiglitazone may offer a modest benefit in the treatment of atopic dermatitis. A well designed, randomized controlled trial is needed to establish safety and efficacy. ^[60]
- * **Crohn’s disease** – a small, randomized, blinded, controlled trial suggests that rosiglitazone may offer a modest benefit in the treatment of patients with Crohn’s disease. Larger, well designed, randomized controlled trials are needed to establish safety and efficacy for this indication. ^[59]
- * **Gliomas** – a small, randomized controlled trial evaluated pioglitazone + rofecoxib when added to chemotherapy in 14 patients with high-grade gliomas. There was a modest effect noted, but larger, well designed randomized controlled trials are needed to establish safety and efficacy for this indication. ^[63]
- * **HIV-related lipoatrophy** – A randomized placebo-controlled trial failed to show a significant benefit from rosiglitazone in lipoatrophy or metabolic parameters in patients with HIV-related lipoatrophy. ^[62]
- * **Type 1 diabetes** – The FDA approved package insert warns that both rosiglitazone and pioglitazone exerts their antihyperglycemic effect only in the presence of insulin. Therefore, neither agent should be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Small randomized trials have suggested a possible benefit of TZDs administered with insulin in patients with type 1 diabetes, but larger, well-designed, randomized, controlled trials are needed to establish safety and efficacy. ^[11-14, 27, 57, 61]
- * **Pre-diabetes** – A large randomized, double-blind, placebo-controlled trial (DREAM) evaluated rosiglitazone in 5,269 adults with impaired glucose tolerance or impaired fasting glucose (pre-diabetes).^[32,33] Limitations to the validity and usefulness of this study include:
 - High number of patient drop-outs (~23%), which erodes randomization creates uncertainty as to whether the treatment groups were comparable by the end of the study.
 - The clinical relevance of the co-primary endpoint is uncertain as rosiglitazone

resulted in no significant improvement in the incidence of any cardiovascular endpoint or in the incidence of death during the trial.

- Rosiglitazone resulted in a statistically significant increase in heart failure (0.5% vs. 0.1%, HR 7.03, P=0.01) compared to placebo, despite having excluded patients with significant pre-existing CV disease.

Safety

- The FDA approved package insert for both pioglitazone and rosiglitazone contains a black box warning advising that thiazolidinediones cause or exacerbate congestive heart failure in some patients. Patients should be observed for signs and symptoms of heart failure after initiation.^[11-14, 27, 57]
 - * Administration of pioglitazone to patients with NYHA functional class II/III heart failure was associated with a statistically significant increase in the composite primary endpoint of cardiovascular mortality and hospitalization or ER visits for heart failure.^[74]
- The FDA approved package insert for rosiglitazone warns that a meta-analysis of 42 clinical trials showed that rosiglitazone was associated for an increased risk of myocardial ischemic events such as angina and myocardial infarction. Other trials have not confirmed this association.^[11-14, 27, 57, 65-68]
- Dose related weight gain has been observed for both rosiglitazone and pioglitazone, alone and in combination with other hypoglycemic agents.^[11,12]
- Common thiazolidinedione adverse reactions include headache, upper respiratory tract infection, sinusitis, edema, hypoglycemia (especially when combined with other agents) and diarrhea.^[11,12]
- Rosiglitazone does not inhibit any of the major P450 enzymes at clinically relevant concentrations. Pioglitazone may be a weak inducer of CYP450 isoform 3A4 substrate and may interact with other drugs metabolized by the same enzyme.^[11,12]
- Rosiglitazone and pioglitazone may increase the rate of upper arm, hand and foot fractures in female patients with type 2 diabetes.^[31,56]
 - * The hazard ratio for fractures in women at 5 years was 1.81 to 2.13 for rosiglitazone compared to women taking metformin or glyburide, respectively. There was no

apparent increase in fracture risk for men. [78]

Appendix 1: Comparison Of Product Information Reported Reductions In A1C (Monotherapy Only) [11, 12, 79-82]				
Drug	Baseline A1C (%)	Duration of Trial	Mean change from baseline (%)	Placebo Corrected change in A1C (%)
metformin (Glucophage®) up to 2550 mg per day	8.4	29 weeks	-1.4	-1.8
pioglitazone (Actos®) 30 mg to 45 mg daily	10.2 to 10.3	26 weeks	-0.3 to -0.9	-1.0 to -1.6
rosiglitazone (Avandia®) 2 mg bid to 4 mg bid	8.9 to 9.0	26 weeks	-0.1 to -0.7	-0.9 to -1.5
repaglinide (Prandin®) up to 4 mg daily (titration trial)	8.5	12 weeks	-0.6	-1.7
exenatide (Byetta®) 5 to 10 mcg BID (with metformin)	8.2 to 8.3	30 weeks	-0.4 to -0.8	-0.5 to -0.9
glimepiride 8 mg once daily (Amaryl®, generic)	unknown	14 weeks	unknown	-2.0
sitagliptin (Januvia®) 100 mg once daily	8.0	18 to 24 weeks	-0.5 to -0.6	-0.6 to -0.8

*Note: Data are pooled from separate studies or product literature and not necessarily comparable

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Cross References
Avandia [®] , rosiglitazone-containing medications dru132
Januvia [®] , sitagliptin-containing medications (Januvia, Janumet [®]) dru140
Symlin [®] , pramlintide, dru121
Byetta [®] , exenatide, dru120
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Codes	Number	Description
N/A		