

STEP THERAPY POLICY

- POLICY:** Diabetes – Thiazolidinedione Step Therapy Policy
- Actos® (pioglitazone tablets – Takeda, generic)
 - Actoplus Met® (pioglitazone/metformin tablets – Takeda, generic)
 - Duetact® (pioglitazone/glimepiride tablets – Takeda, generic)

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OVERVIEW

Pioglitazone is indicated as adjunct to diet and exercise to improve glycemic control in adults with **type 2 diabetes**.¹

Pioglitazone is also available in combination with other antidiabetic medications, including metformin and a sulfonylurea, as well as a dipeptidyl peptidase-4 (DPP-4) inhibitor. Of note, the combination product alogliptin/pioglitazone (Oseni™, generic) is not targeted in this policy; refer to the *Diabetes – Dipeptidyl Peptidase-4 Inhibitors Step Therapy Policy*.

Guidelines

The American Diabetes Association Standards of Care (2024) note that first-line therapy for type 2 diabetes depends on comorbidities, patient-centered treatment factors, and management needs; it generally includes metformin and comprehensive lifestyle modification.² Very high circulating levels of metformin have been associated with lactic acidosis. However, the occurrence of this complication is now known to be very rare. In patients with contraindications or intolerance to metformin, initial therapy should be based on patient factors. Because type 2 diabetes is often a progressive disease, combination therapy may be needed for many patients over time to achieve glycemic targets.

The choice of medication added to initial therapy is based on the clinical characteristics of the patient.² Important clinical characteristics include the presence of established atherosclerotic cardiovascular disease or indicators of high atherosclerotic cardiovascular disease risk, heart failure, chronic kidney disease, obesity, non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH), and risk for specific adverse drug effects, as well as safety and tolerability. TZDs are among the options in patients with established atherosclerotic cardiovascular disease when hemoglobin A_{1c} remains above target despite therapy with a glucagon-like peptide-1 agonist or sodium glucose co-transporter-2 inhibitor, or when glycemic management is the primary goal of therapy.

Pioglitazone is noted to improve glucose and lipid metabolism and reverse steatohepatitis in patients with prediabetes or type 2 diabetes and NASH, or patients without diabetes with NASH; fibrosis also improved in some trials. Pioglitazone may also result in a resolution of NASH. Further, pioglitazone may slow the pace of fibrosis progression observed in patients with type 2 diabetes and is overall cost-effective for the treatment of NASH. Other guidelines have similar recommendations.^{3,4}

The American Association of Clinical Endocrinologists and American Association for the Study of Liver Diseases guideline for the diagnosis and management of NAFLD in primary care and endocrinology settings (2022) recommends pioglitazone or glucagon-like peptide-1 agonists (semaglutide and liraglutide) in patients with type 2 diabetes and NAFLD to offer cardiometabolic benefit (Grade A; high strength of evidence).⁵ Both pioglitazone and glucagon-like peptide-1 agonists are noted to have proven efficacy to reverse NASH in individuals with obesity, prediabetes, or type 2 diabetes. Due to the lack of evidence of efficacy, metformin (along with several other classes) is not recommended for the treatment of

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steatohepatitis (no benefit necrosis or inflammation) but may be continued as needed for the treatment of hypoglycemia in individuals with type 2 diabetes and NAFLD/NASH (Grade B; high strength of evidence). A guideline from the American Gastroenterological Association has similar recommendations for pioglitazone in the setting of NASH/NAFLD.⁶

POLICY STATEMENT

This program has been developed to encourage the use of a Step 1 Product prior to the use of a Step 2 Product. If the Step Therapy rule is not met for a Step 2 Product at the point of service, coverage will be determined by the Step Therapy criteria below. All approvals are provided for 1 year in duration.

Automation: A patient with a of one of the following within the 130-day look-back period is excluded from Step Therapy:

- One Step 1 Product; OR
- One of the following metformin-containing products: Glumetza ER, metformin oral solution, Riomet, Riomet ER, metformin extended-release (generics to Fortamet and Glumetza), glyburide/metformin, glipizide/metformin, Janumet, sitagliptin/metformin (authorized generic), Janumet XR, Jentadueto, Jentadueto XR, Kombiglyze XR, saxagliptin/metformin extended-release, pioglitazone/metformin, pioglitazone/glimeperide, Kazano, alogliptin/metformin, Invokamet, Invokamet XR, Synjardy, Synjardy XR, Xigduo XR, Segluromet.

Step 1: generic metformin, generic metformin extended-release (generic to Glucophage XR only)

Step 2: Actos (brand only), Actoplus Met (brand only), Duetact (brand only)

CRITERIA

1. If the patient has tried one Step 1 Product, approve a Step 2 Product.

Note: A trial of one of the following metformin-containing products also satisfies the requirement: Glucophage (obsolete), Glucophage XR (obsolete), Glumetza ER, Fortamet ER (obsolete), metformin oral solution, Riomet, Riomet ER, metformin extended-release (generics to Fortamet ER and Glumetza ER), glyburide/metformin, glipizide/metformin, Janumet, sitagliptin/metformin (authorized generic), Janumet XR, Jentadueto, Jentadueto XR, repaglinide/metformin (obsolete), Kombiglyze XR, saxagliptin/metformin extended-release, pioglitazone/metformin, pioglitazone/glimeperide, Kazano, alogliptin/metformin, Invokamet, Invokamet XR, Synjardy, Synjardy XR, Xigduo XR, Segluromet.

2. If the patient has non-alcoholic steatohepatitis/metabolic-dysfunction associated steatohepatitis or non-alcoholic fatty liver disease/metabolic-dysfunction associated steatotic liver dysfunction, approve Actos.
3. No other exceptions are recommended.

REFERENCES

1. Actos[®] tablets [prescribing information]. Deerfield, IL: Takeda; June 2020.
2. American Diabetes Association. Standards of care in diabetes – 2024. *Diabetes Care*. 2024;47(1):S1-S328.
3. Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology clinical practice guideline: developing a diabetes mellitus comprehensive care plan – 2022 update. *Endocr Pract*. 2022;18:923-1049.
4. Samson SL, Vellanki P, Blonde L, et al. American Association of Clinical Endocrinology consensus statement: comprehensive type 2 diabetes management algorithm – 2023 update. *Endocr Pract*. 2023;29:305-340.
5. Cusi K, Isaacs S, Bard D, et al. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Settings. Co-sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract*. 2022;28:528-562.
6. Kanwai F, Shubrook JH, Adams LA, et al. Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. *Gastroenterol*. 2021;161:1657-1669.