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)

REVIEW DATE: 05/15/2024; selected revision 08/07/2024

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

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 if 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 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.

- 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)

Diabetes – Thiazolidinedione Step Therapy product(s) is(are) covered as medically necessary when the following step therapy criteria is(are) met. Any other exception is considered not medically necessary.

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.

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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Automation:** The following products were removed from the automation (obsolete): Glucophage, Glucophage XR, repaglinide/metformin, Actoplus Met XR. Glumetza and Fortamet were clarified to be Glumetza ER and Fortamet ER. Pioglitazone was removed from the list of metformin-containing products, as it does not contain metformin and is not intended to count for approval of a Step 2 product. **Step 2 Products**: Actoplus Met XR was removed from the Step 2 products; this product is obsolete. **Criteria:** For patients requesting a Step 1 product requesting a Step 2 product, the note was updated to reflect that Glucophage, Glucophage XR, repaglinide/metformin, and Actoplus Met XR are obsolete (these still count towards a trial of a Step 1 product). Additionally Glumetza and Fortamet were clarified to be Glumetza ER and Fortamet ER. Pioglitazone was removed from the list of metformin-containing products, as it does not contain metformin and is not intended to count for approval of a Step 2 product. Criteria were added to approve Actos for patients with non-alcoholic steatohepatitis. Previously, this condition was not addressed.	05/17/2023
Selected Revision	**Automation:** Saxagliptin/metformin extended-release (generic to Kombiglyze XR) was added to the list of metformin-containing products.	09/13/2023
Annual Revision	**Automation:** Fortamet ER was removed from the list of metformin-containing products (obsolete). **Step 2 Products:** Avandia was removed (obsolete). Clarification was added that for the Step 2 products, only the brand is in Step 2. **Criteria:** For a patient requesting a Step 2 product, the note was updated to reflect that Fortamet ER is obsolete (this still	05/15/2024

	counts towards a trial of a Step 1 product). Criteria for a patient with non-alcoholic steatohepatitis was updated to approve Actos for a patient with non-alcoholic steatohepatitis/metabolic-dysfunction associated steatohepatitis or non-alcoholic fatty liver disease/metabolic-dysfunction associated steatotic liver disease.	
Selected Revision	**Automation:** Sitagliptin/metformin (authorized generic) was added to automation for one metformin-containing product. **Criteria:** For a patient requesting a Step 2 product, the note was updated to add sitagliptin/metformin (authorized generic) to the list of metformin-containing products.	08/07/2024