



STEP THERAPY POLICY

- POLICY:** Diabetes – Dipeptidyl Peptidase-4 Inhibitors Step Therapy Policy
- Janumet[®] (sitagliptin/metformin tablets – Merck)
 - Janumet[®] XR (sitagliptin/metformin extended-release tablets – Merck)
 - Januvia[®] (sitagliptin tablets – Merck)
 - Jentadueto[®] (linagliptin/metformin tablets – Boehringer Ingelheim)
 - Jentadueto[®] XR (linagliptin/metformin extended-release tablets – Boehringer Ingelheim)
 - Kazano[™] (alogliptin/metformin tablets – Takeda, authorized generic)
 - Kombiglyze[®] XR (saxagliptin/metformin extended-release tablets – AstraZeneca, generic)
 - Nesina[®] (alogliptin tablets – Takeda, authorized generic)
 - Onglyza[®] (saxagliptin tablets – AstraZeneca, generic)
 - Oseni[™] (alogliptin/pioglitazone tablets – Takeda, authorized generic)
 - Tradjenta[®] (linagliptin tablets – Boehringer Ingelheim)
 - Zituvio[™] (sitagliptin tablets – Zydus, authorized generic)

REVIEW DATE: 05/22/2024

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CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

The dipeptidyl peptidase-4 (DPP-4) inhibitors and combination products are indicated to improve glycemic control in adults with **type 2 diabetes mellitus** (as

monotherapy and as combination therapy) when used as adjuncts to diet and exercise.^{1-11,15}

Various combination products are available which combine DPP-4 inhibitors with metformin, sodium glucose co-transporter-2 (SGLT-2) inhibitors, and/or thiazolidinediones (TZDs). Of note, the SGLT-2/DPP-4 combination products are not addressed in this policy; refer to the *Diabetes – Sodium Glucose Co-Transporter-2 and Dipeptidyl Peptidase-4 Inhibitors Step Therapy Policy*.

GUIDELINES

The American Diabetes Association Standards of Care (2024) note that therapy for patients with type 2 diabetes depends on comorbidities, patient-centered treatment factors, and management needs and generally includes metformin and comprehensive lifestyle modification.¹² 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. Metformin is contraindicated in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²) and in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.¹⁴ DPP-4 inhibitors are among the classes of medications recommended as add-on therapy after metformin (or as initial therapy if metformin cannot be used). Because type 2 diabetes is often a progressive disease, combination therapy may be needed for many patients over time to achieve glycemic targets. Other guidelines have similar recommendations.^{13,16}

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, Riomet, metformin oral solution, Riomet ER, metformin extended-release (generics to Fortamet ER and Glumetza ER), glyburide/metformin, glipizide/metformin, Actoplus Met, pioglitazone/metformin, Invokamet, Invokamet XR, Synjardy, Synjardy XR, Xigduo XR, dapagliflozin/metformin extended-release (authorized generic to Xigduo XR), Segluromet; OR
- One Step 2 Product.

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

Step 2: Januvia, Janumet, Janumet XR, saxagliptin (Onglyza, generic), saxagliptin/metformin extended-release (Kombiglyze XR, generic), Tradjenta, Jentadueto, Jentadueto XR, alogliptin (Nesina, authorized generic), alogliptin/metformin (Kazano, authorized generic), alogliptin/pioglitazone (Oseni, authorized generic), sitagliptin (Zituvio, authorized generic)

Diabetes – Dipeptidyl Peptidase-4 Inhibitors 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: Fortamet ER (obsolete), Glucophage (obsolete), Glucophage XR (obsolete), Glumetza ER, Riomet, metformin oral solution, Riomet ER, metformin extended-release (generics to Fortamet ER and Glumetza ER), glyburide/metformin, glipizide/metformin, Actoplus Met, pioglitazone/metformin, Actoplus Met XR (obsolete), repaglinide/metformin (obsolete), Invokamet, Invokamet XR, Synjardy, Synjardy XR, Xigduo XR, dapagliflozin/metformin extended-release (authorized generic to Xigduo XR), Segluromet.
- 2.** If the patient has tried one Step 2 Product, approve the requested Step 2 Product.
- 3.** If the patient is initiating dual (combination) therapy with a single-entity DPP-4 inhibitor (Januvia, saxagliptin [Onglyza, generic], Tradjenta, alogliptin [Nesina, authorized generic], or sitagliptin [Zituvio, authorized generic]) AND metformin, approve a single-entity DPP-4 inhibitor.
- 4.** If the patient has a contraindication to metformin, according to the prescriber, approve a single-entity DPP-4 inhibitor.
Note: Examples of contraindications to metformin include acute or chronic metabolic acidosis, including diabetic ketoacidosis.

REFERENCES

1. Janumet® tablets [prescribing information]. Whitehouse Station, NJ: Merck; June 2022.
2. Janumet® XR tablets [prescribing information]. Whitehouse Station, NJ: Merck; June 2022.
3. Januvia® tablets [prescribing information]. Rahway, NJ: Merck; December 2023.
4. Jentadueto® tablets [prescribing information]. Ridgefield, CT: Boehringer Ingelheim; June 2023.
5. Jentadueto® XR tablets [prescribing information]. Ridgefield, CT: Boehringer Ingelheim; June 2023.

6. Kazano™ tablets [prescribing information]. Lexington, MA: Takeda; July 2023.
7. Kombiglyze® XR tablets [prescribing information]. Wilmington, DE: AstraZeneca; July 2019.
8. Nesina® tablets [prescribing information]. Lexington, MA: Takeda; July 2023.
9. Onglyza® tablets [prescribing information]. Wilmington, DE: AstraZeneca; June 2019.
10. Oseni™ tablets [prescribing information]. Lexington, MA: Takeda; March 2022.
11. Tradjenta® tablets [prescribing information]. Ridgefield, CT: Boehringer Ingelheim; June 2023.
12. American Diabetes Association – standards of care in diabetes – 2024. *Diabetes Care*. 2024;47(Suppl 1):S1-S321.
13. 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.
14. Metformin tablets [prescribing information]. Raleigh, NC: Indicus Pharma; June 2020.
15. Zituvio™ tablets [prescribing information]. Pennington, NJ: Zydus; October 2023.
16. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	<p>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.</p> <p>Criteria: For patients 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.</p>	05/03/2023
Selected Revision	<p>Step 2 Products: Saxagliptin (generic to Onglyza) and saxagliptin/metformin extended-release (generic to Kombiglyze XR) were added to Step 2 products.</p> <p>Criteria: For a patient initiating dual (combination) therapy with a single-entity DPP-4 inhibitor AND metformin, saxagliptin was added to the list of single-entity DPP-4 inhibitors to approve.</p>	09/13/2023
Selected Revision	<p>Step 2 Products: Zituvio was added to the list of Step 2 products.</p> <p>Criteria: For a patient initiating dual (combination) therapy with a single-entity DPP-4 inhibitor AND metformin, Zituvio was added to the list of single-entity DPP-4 inhibitors to approve.</p>	02/07/2024
Annual Revision	<p>Automation: Fortamet ER was removed from the list of metformin-containing products (obsolete). Dapagliflozin/metformin extended-release (authorized generic to Xigduo XR) was added to the list of metformin-containing products.</p> <p>Step 2 Products: sitagliptin (authorized generic to Zituvio) was added to Step 2 products.</p> <p>Criteria: For a patient requesting a Step 2 product, the note was updated to reflect that Fortamet ER is obsolete (this still counts towards a trial of a Step 1 product). The note was also updated to add dapagliflozin/metformin extended-release (authorized generic to Xigduo XR). For a patient initiating dual (combination) therapy with a single-entity DPP-4 inhibitor AND</p>	05/22/2024

	metformin, sitagliptin (authorized generic to Zituvio) was added to the list of single-entity DPP-4 inhibitors to approve.	
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