

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/Eli Lilly)
 - Jentadueto[®] XR (linagliptin/metformin extended-release tablets – Boehringer Ingelheim/Eli Lilly)
 - Kazano[™] (alogliptin/metformin tablets – Takeda, authorized generic)
 - Kombiglyze[®] XR (saxagliptin/metformin extended-release tablets – AstraZeneca)
 - Nesina[®] (alogliptin tablets – Takeda, authorized generic)
 - Onglyza[®] (saxagliptin tablets – AstraZeneca)
 - Oseni[™] (alogliptin/pioglitazone tablets – Takeda, authorized generic)
 - Tradjenta[®] (linagliptin tablets – Boehringer Ingelheim/Eli Lilly)

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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 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 (2020) recommend metformin as initial therapy for most patients with type 2 diabetes, unless contraindications to metformin are present.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. Any of several classes of medications, including DPP-4 inhibitors, SGLT-2 inhibitors, and TZDs, may be used as add-on therapy after metformin (or as initial therapy if metformin cannot be used). Because type 2 diabetes is a progressive disease in many patients, combination therapy may be needed for many patients over time to achieve glycemic targets. Other guidelines have similar recommendations.¹³

SAFETY

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 There have been post-marketing cases of metformin-associated lactic acidosis, including fatal cases. Metformin decreases liver uptake of lactate, increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk. Hypoxic states (e.g., acute congestive heart failure, cardiovascular collapse, acute myocardial infarction, sepsis), excessive alcohol intake, and hepatic impairment are noted in the metformin prescribing information as among the risk factors for development of lactic acidosis.

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 history of one Step 1 Product within the 130-day look-back period is excluded from Step Therapy. Additionally, a patient with a history of one DPP-4 inhibitor (e.g., Januvia, Nesina, alogliptin, Onglyza, Tradjenta), or a DPP-4 containing product (e.g., Janumet, Janumet XR, Oseni, alogliptin/pioglitazone, Kazano, alogliptin/metformin, Kombiglyze XR, Jentadueto, Jentadueto XR) within the 130-day look-back period is excluded from Step Therapy.

Step 1: metformin, metformin extended-release, Glucophage, Glucophage XR, Glumetza, Fortamet, Riomet, metformin oral solution, Riomet ER, Avandamet, Actoplus Met, pioglitazone/metformin, Actoplus Met XR, Glucovance, metformin/glyburide, Prandimet, repaglinide/metformin, metformin/glipizide, Invokamet, Invokamet XR, Synjardy, Synjardy XR, Xigduo XR, Segluromet

Step 2: Januvia, Janumet, Janumet XR, Onglyza, Kombiglyze XR, Tradjenta, Jentadueto, Jentadueto XR, Nesina, alogliptin, Kazano, alogliptin/metformin, Oseni, alogliptin/pioglitazone

CRITERIA

1. If the patient has tried one Step 1 Product, approve a Step 2 Product.
2. If the patient is already started on a dipeptidyl peptidase-4 (DPP-4) inhibitor, approve a Step 2 Product.
3. If the patient is initiating dual (combination) therapy with Januvia, Onglyza, Tradjenta, Nesina or alogliptin 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).
5. No other exceptions are recommended.

REFERENCES

1. Janumet[®] tablets [prescribing information]. Whitehouse Station, NJ: Merck; August 2019.
2. Janumet[®] XR tablets [prescribing information]. Whitehouse Station, NJ: Merck; August 2019.
3. Januvia[®] tablets [prescribing information]. Whitehouse Station, NJ: Merck; August 2019.
4. Jentadueto[®] tablets [prescribing information]. Ridgefield, CT and Indianapolis, IN: Boehringer Ingelheim/Eli Lilly; July 2019.
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6. Kazano[™] tablets [prescribing information]. Deerfield, IL: Takeda; July 2019.
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11. Tradjenta[®] tablets [prescribing information]. Ridgefield, CT and Indianapolis, IN: Boehringer Ingelheim/Eli Lilly; July 2019.
12. American Diabetes Association. Standards of medical care in diabetes – 2020. *Diabetes Care*. 2020;43(Suppl 1):S1-S12. Available at: https://care.diabetesjournals.org/content/43/Supplement_1. Accessed on March 18, 2020.

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14. Glucophage[®] and Glucophage[®] XR [prescribing information]. Princeton, NJ: Bristol-Meyers Squibb; May 2018.