STEP THERAPY POLICY

POLICY: Diabetes – Sodium Glucose Co-Transporter-2 and Dipeptidyl Peptidase-4 Inhibitors Step Therapy Policy

- Glyxambi® (empagliflozin and linagliptin tablets – Boehringer Ingelheim)
- Qtern® (dapagliflozin and saxagliptin tablets – AstraZeneca)
- Steglujan® (ertugliflozin and sitagliptin tablets – Merck)
- Trijardy® XR (empagliflozin, linagliptin, and metformin extended-release tablets – Boehringer Ingelheim)

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OVERVIEW

Glyxambi, Qtern, Steglujan, and Trijardy XR are sodium glucose co-transporter-2 inhibitor (SGLT-2) and dipeptidyl peptidase-4 (DPP-4) inhibitor combination products indicated as an adjunct to diet and exercise to improve glycemic control in adults with **type 2 diabetes mellitus**; Trijardy XR also contains metformin.[1-4] Various single-entity SGLT-2 inhibitors and DPP-4 inhibitors are available. In addition to their indications for type 2 diabetes, Jardiance® (empagliflozin tablets), Invokana® (canagliflozin tablets), and dapagliflozin (Farxiga®, authorized generic) possess indications related to cardiovascular, renal, and/or heart failure benefits. Efficacy of the SGLT-2/DPP-4 inhibitor combination products has not been established in these settings. Refer to Table 1 for a summary of the available products containing SGLT-2 and/or DPP-4 inhibitors.

Table 1. SGLT-2 and DPP-4 inhibitor-containing combination products.

Table 1 (continued). SGLT-2 and DPP-4 inhibitor-containing combination products.
SGLT-2 – Sodium glucose co-transporter-2; DPP-4 – Dipeptidyl peptidase-4; CANA – canagliflozin; DAPA – dapagliflozin; EMPA – empagliflozin; ERTU – ertugliflozin; ALO – alogliptin; LINA – linagliptin; SAXA – saxagliptin; SITA – sitagliptin; XR – extended-release.

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.[5] Pharmacologic approaches, specified as metformin or agent(s), including combination therapy, that provide adequate efficacy to achieve and maintain treatment goals should be considered. For patients with type 2 diabetes and established atherosclerotic cardiovascular disease (ASCVD) or indicators of high ASCVD risk, heart failure, or chronic kidney disease, an SGLT-2 inhibitor and/or glucagon-like peptide-1 receptor agonist with demonstrated cardiovascular disease benefit is recommended independent of hemoglobin A_{1c} or metformin use, and in consideration of patient-specific factors.

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.[5] 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 m^2) and in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.[7] DPP-4 inhibitors and SGLT-2 inhibitors are among the classes of medications recommended as add-on therapy after metformin (or as initial therapy if metformin cannot be used).[5] 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.[6,8]

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, Riomet, metformin oral solution, Riomet ER, metformin extended-release (generics to Fortamet ER and Glumetza ER), metformin/glyburide, metformin/glipizide, Actoplus Met, pioglitazone/metformin, Janumet, sitagliptin/metformin (authorized generic), Janumet XR, Kombiglyze XR, saxagliptin/metformin extended-release, Jentadueto, Jentadueto XR, Kazano, aloglitpin/metformin (authorized generic to Kazano), Synjardy, Synjardy XR, Xigduo XR, dapagliflozin/metformin extended-release (authorized generic to Xigduo XR), Invokamet, Invokamet XR, Segluromet; OR
- One of the following DPP-4 inhibitor products: Januvia, Nesina, alogliptin (authorized generic to Nesina), Onglyza, saxagliptin, Tradjenta, Oseni, alogliptin/pioglitazone (authorized generic to Oseni), Zituvio, sitagliptin (authorized generic to Zituvio); OR
- One SGLT-2 inhibitor (Brenzavvy, Farxiga, dapagliflozin [authorized generic to Farxiga], Invokana, Jardiance, Steglatro).

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

Step 2: Glyxambi, Qtern, Steglujan, Trijardy XR

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), Riomet, metformin oral solution, Riomet ER, metformin extended-release (generics to Fortamet ER and Glumetza ER), metformin/glyburide, metformin/glipizide, Actoplus Met, pioglitazone/metformin, Actoplus Met XR (obsolete), Janumet, sitagliptin/metformin (authorized generic), Janumet XR, repaglinide/metformin (obsolete), Kombiglyze XR, saxagliptin/metformin extended-release, Jentadueto, Jentadueto XR, Kazano, aloglitpin/metformin (authorized generic to Kazano), Synjardy, Synjardy XR, Xigduo XR, dapagliflozin/metformin extended-release (authorized generic to Xigduo XR), Invokamet, Invokamet XR, Segluromet.

2. If the patient has tried a DPP-4 inhibitor, a DPP-4 inhibitor-containing product, or an SGLT-2 inhibitor, other than Glyxambi, Qtern, Steglujan, or Trijardy XR, approve a Step 2 Product.
Note: Examples of DPP-4 inhibitors include but are not limited to Januvia, Nesina, alogliptin (authorized generic to Nesina), Onglyza, saxagliptin, Tradjenta, Zituvio, and sitagliptin (authorized generic to Zituvio). Examples of DPP-4 inhibitor-containing products include but are not limited to Oseni and alogliptin/pioglitazone (authorized generic to Oseni). Examples of SGLT-2 inhibitors include but are not limited to Brenzavvy, Farxiga, dapagliflozin (authorized generic to Farxiga), Invokana, Jardiance, Steglatro.

3. If the patient has a contraindication to metformin, according to the prescriber, approve Glyxambi, Qtern, or Steglujan.
Note: Examples of contraindications to metformin include acute or chronic metabolic acidosis, including diabetic ketoacidosis.

4. No other exceptions are recommended.

REFERENCES

1. Glyxambi® tablets [prescribing information]. Ridgefield, CT: Boehringer Ingelheim; October 2023.
2. Qtern® tablets [prescribing information]. Wilmington, DE: AstraZeneca; September 2023.
3. Steglujan® tablets [prescribing information]. Whitehouse Station, NJ: Merck; September 2023.
4. Trijardy® XR tablets [prescribing information]. Ridgefield, CT: Boehringer Ingelheim; October 2023.
5. American Diabetes Association. Standards of medical care in diabetes – 2024. *Diabetes Care*. 2024;47(Suppl 1):S1-S321.
6. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2022;45(11):2753-2786.
7. Metformin tablets [prescribing information]. Raleigh, NC: Indicus; June 2020.
8. 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.