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** when treatment with the individual components of the combination is appropriate; 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 Farxiga® (dapagliflozin tablets) possess indications related to cardiovascular (CV), renal, and/or heart failure benefits. Efficacy of the SGLT-2 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.

	SGLT-2 Component				DPP-4 Inhibitor Component				Metformin
	CANA	DAPA	EMPA	ERTU	ALO	LINA	SAXA	SITA	
DPP-4 inhibitor and metformin									
Janumet								X	X
Janumet XR								X	X
Jentadueto						X			X
Jentadueto XR						X			X
Kazano, authorized generic					X				X
Kombiglyze XR							X		X
DPP-4 inhibitor and other									
Oseni (alogliptin/ pioglitazone, authorized generic)					X				
SGLT-2 inhibitor and metformin									
Invokamet	X								X
Invokamet XR	X								X
Segluromet				X					X
Synjardy			X						X
Synjardy XR			X						X
Xigduo XR		X							X
SGLT-2 inhibitor and DPP-4 inhibitor									
Glyxambi			X			X			
Qtern		X					X		
Steglujan				X				X	
Trijardy XR			X			X			X

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 (2020) recommend metformin as initial therapy for most patients with type 2 diabetes, unless contraindications to metformin are present.[5] 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. 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). 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.[6]

SAFETY

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] 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 among the risk factors for development of lactic acidosis.

The SGLT-2 inhibitors generally contain similar Warnings related to risk of hypotension, ketoacidosis, genital mycotic infections, and Fournier's gangrene.[1-4] Invokana has a unique Boxed Warning regarded increased risk of lower limb amputations. DPP-4 inhibitors have Warnings related to pancreatitis, heart failure, arthralgia, and bullous pemphigoid. Glyxambi, Qtern, Steglujan, and Trijardy XR should not be used in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2 for Steglujan; eGFR < 45 mL/min/1.73 m^2 for Glyxambi, Trijardy XR, and Qtern).

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), Oseni, alogliptin/pioglitazone, or one SGLT-2 inhibitor (e.g., Farxiga, Invokana, Jardiance, Steglatro) 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, Glucovance, metformin/glyburide, Avandamet, metformin/glipizide, Actoplus Met, pioglitazone/metformin, Actoplus Met XR, Janumet, Janumet XR, Prandimet, repaglinide/metformin, Kombiglyze XR, Jentadueto, Jentadueto XR, Kazano, aloglitpin/metformin, Synjardy, Synjardy XR, Xigduo XR, Invokamet, Invokamet XR, Segluromet

Step 2: Glyxambi, Qtern, Steglujan, Trijardy XR

CRITERIA

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

2. If the patient has tried a DPP-4 inhibitor (e.g., Januvia, Nesina, alogliptin, Onglyza, Tradjenta), DPP-4 inhibitor-containing product (e.g., Oseni, alogliptin/pioglitazone), or an SGLT-2 inhibitor (e.g., Farxiga, Invokana, Jardiance, Steglatro), other than Glyxambi, Qtern, Steglujan, or Trijardy XR, approve a Step 2 Product.

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® [prescribing information]. Ridgefield, CT: Boehringer Ingelheim; January 2020.
2. Qtern® [prescribing information]. Wilmington, DE: AstraZeneca; January 2020.
3. Steglujan™ [prescribing information]. Whitehouse Station, NJ: Merck; January 2020.
4. Trijardy™ XR [prescribing information]. Ridgefield, CT: Boehringer Ingelheim; January 2020.
5. American Diabetes Association. Standards of medical care in diabetes – 2020. *Diabetes Care*. 2020;43(Suppl 1):S1-S212. Available at: https://care.diabetesjournals.org/content/43/Supplement_1. Accessed on March 18, 2020.
6. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2020 executive summary. *Endocr Pract*. 2020;26(1):107-139. Available at: https://www.aace.com/sites/all/files/diabetes-algorithm-executive-summary.pdf. Accessed on: May 7, 2020.
7. Glucophage® and Glucophage® XR [prescribing information]. Princeton, NJ: Bristol-Meyers Squibb; May 2018.