# Clinical Policy: Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Reference Number: CP.PMN.03
Effective Date: 09.19.18
Last Review Date: 02.20
Line of Business: Medicaid

Revision Log

**See Important Reminder at the end of this policy for important regulatory and legal information.**

## Description

The following agents contain a dipeptidyl peptidase-4 (DPP-4) inhibitor and require prior authorization: linagliptin (Tradjenta®), linagliptin/empagliflozin (Glyxambi®), linagliptin/empagliflozin/metformin (Trijardy™ XR), linagliptin/metformin (Jentadueto®, Jentadueto® XR), saxagliptin (Onglyza®), saxagliptin/dapagliflozin (Qtern®), saxagliptin/dapagliflozin/metformin (Qternmet® XR), saxagliptin/metformin (Kombiglyze® XR), sitagliptin (Januvia®), sitagliptin/ertugliflozin (Steglujan™), and sitagliptin/metformin (Janumet®, Janumet® XR).

## FDA Approved Indication(s)

DPP-4 inhibitors are indicated as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Dapagliflozin- and empagliflozin-containing products are also indicated in adult patients with type 2 diabetes mellitus and established cardiovascular disease (or multiple cardiovascular risk factors [*dapagliflozin only*]) to:

- Reduce the risk of hospitalization for heart failure (HF) (dapagliflozin)
- Reduce the risk of cardiovascular death (empagliflozin)

Limitation(s) of use:

- DPP-4 inhibitors should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
- DPP-4 inhibitors have not been studied in patients with a history of pancreatitis.
- Qternmet XR initiation is intended only for patients currently taking metformin.

## Policy/Criteria

*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

It is the policy of health plans affiliated with Centene Corporation® that DPP-4 inhibitors are **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria**

**A. Type 2 Diabetes Mellitus** (must meet all)**:**

1. Diagnosis of type 2 diabetes mellitus;
2. Age ≥ 18 years;
3. Member meets one of the following (a or b):

a. Failure of ≥ 3 consecutive months of metformin, unless contraindicated or clinically significant adverse effects are experienced;
b. HbA1c drawn within the past 3 months is ≥ 8.5%, and concurrent use of metformin unless contraindicated or clinically significant adverse effects are experienced;

4. If request is for Glyxambi, Qtern, Qternmet XR, Steglujan, or Trijardy XR, member meets one of the following (a, b, or c):
   a. Failure of ≥ 3 consecutive months of Steglatro™ or Segluromet™, unless both are contraindicated or clinically significant adverse effects are experienced;
   b. Member has established cardiovascular disease (e.g., ASCVD or HF) or diabetic nephropathy, and request is for Glyxambi, Qtern, Qternmet XR, or Trijardy XR;
   c. Member has multiple risk factors for cardiovascular disease (*see Appendix D)*, and request is for Qtern or Qternmet XR;
5. If request is for a non-preferred DPP-4 inhibitor other than Glyxambi, Qtern, Qternmet XR, Steglujan, or Trijardy XR, failure of ≥ 3 consecutive months of an alogliptin-containing product (e.g., alogliptin [Nesina®], alogliptin/metformin [Kazano®], alogliptin/pioglitazone [Oseni®]), unless all are contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed the FDA approved maximum recommended dose (*see Section V*).

**Approval duration: 12 months**

**B. Other diagnoses/indications**

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid.

## II. Continued Therapy

**A. Type 2 Diabetes Mellitus** (must meet all)**:**

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed the FDA approved maximum recommended dose (*see Section V*).

**Approval duration: 12 months**

**B. Other diagnoses/indications** (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   **Approval duration: Duration of request or 12 months (whichever is less)**; or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid.

**III. Diagnoses/Indications for which coverage is NOT authorized:**

**A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.PMN.53 for Medicaid or evidence of coverage documents.

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

AACE: American Association of Clinical Endocrinologists
ACE: American College of Endocrinology
ADA: American Diabetes Association
DPP-4: dipeptidyl peptidase-4
FDA: Food and Drug Administration
GLP-1: glucagon-like peptide-1
HbA1c: glycated hemoglobin
SGLT2: sodium-glucose co-transporter 2

*Appendix B: Therapeutic Alternatives*

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.*

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| metformin (Fortamet®, Glucophage®, Glucophage® XR, Glumetza®) | Regular-release (Glucophage): 500 mg PO BID or 850 mg PO QD; increase as needed in increments of 500 mg/week or 850 mg every 2 weeks<br><br>Extended-release:<br>• Fortamet, Glumetza: 1,000 mg PO QD; increase as needed in increments of 500 mg/week<br>• Glucophage XR: 500 mg PO QD; increase as needed in increments of 500 mg/week | Regular-release: 2,550 mg/day<br><br>Extended-release: 2,000 mg/day |
| Segluromet (ertugliflozin/ metformin) | Individualized dose PO BID | 15/2,000 mg/day |
| Steglatro (ertugliflozin) | 5 mg PO QD | 15 mg/day |
| Nesina (alogliptin) | 25 mg PO QD | 25 mg/day |
| Kazano (alogliptin/ metformin) | Individualized dose PO BID | 25/2,000 mg/day |
| Oseni (alogliptin/ pioglitazone) | Individualized dose PO QD | 25/45 mg/day |

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

*Appendix C: Contraindications/Boxed Warnings*

- Contraindication(s):
  - History of serious hypersensitivity reaction to the requested drug product

- Severe renal impairment (*metformin-containing products and Glyxambi*) or moderate to severe renal impairment (*Qtern and Qternmet XR*)
- End-stage renal disease or dialysis (*Glyxambi only*)
- Metabolic acidosis, including diabetic ketoacidosis (*metformin-containing products only*)

- Boxed warning(s): lactic acidosis (*metformin-containing products only*)

*Appendix D: General Information*

- A double-blind, placebo-controlled dose-response trial by Garber et al. found the maximal efficacy of metformin to occur at doses of 2,000 mg. However, the difference in adjusted mean change in HbA1c between the 1,500 and 2,000 mg doses was 0.3%, suggesting that the improvement in glycemic control provided by the additional 500 mg may be insufficient when HbA1c is > 7%.
- Per the 2019 American Diabetes Association (ADA) and American Association of Clinical Endocrinologists and 2019 American College of Endocrinology (AACE/ACE) guidelines:
  - Metformin is recommended for all patients with type 2 diabetes. Monotherapy is recommended for most patients; however:
    - Starting with dual therapy (i.e., metformin plus another agent, such as a sulfonylurea, thiazolidinedione, DPP-4 inhibitor, sodium-glucose co-transporter 2 [SGLT2] inhibitor, glucagon-like peptide 1 [GLP-1] receptor agonist, or basal insulin) may be considered for patients with baseline HbA1c ≥ 1.5% above their target per the ADA (≥ 7.5% per the AACE/ACE). According to the ADA, a reasonable HbA1c target for many non-pregnant adults is < 7% (≤ 6.5% per the AACE/ACE).
    - Starting with combination injectable therapy (i.e., with GLP-1 receptor agonist or insulin) may be considered for patients with baseline HbA1c ≥ 10% or ≥ 2% above their target per the ADA (> 9% if symptoms are present per the AACE/ACE).
  - If the target HbA1c is not achieved after approximately 3 months of monotherapy, dual therapy should be initiated. If dual therapy is inadequate after 3 months, triple therapy should be initiated. Finally, if triple therapy fails to bring a patient to goal, combination injectable therapy should be initiated. Each non-insulin agent added to initial therapy can lower HbA1c by 0.7-1%.
- Examples of cardiovascular risk factors may include but are not limited to: dyslipidemia, hypertension, obesity, a family history of premature coronary disease, and smoking.
- According to the ADA, ASCVD includes coronary heart disease, cerebrovascular disease, or peripheral arterial disease presumed to be of atherosclerotic origin.

## V. Dosage and Administration

| Drug Name | Dosing Regimen | Maximum Dose |
|---|---|---|
| Glyxambi (linagliptin/empagliflozin) | 5/10 mg PO QD | 5/25 mg/day |
| Janumet (sitagliptin/metformin) | Individualized dose PO BID | 100/2,000 mg/day |
| Janumet XR (sitagliptin/metformin) | Individualized dose PO QD | 100/2,000 mg/day |
| Januvia (sitagliptin) | 100 mg PO QD | 100 mg/day |
| Jentadueto (linagliptin/metformin) | Individualized dose PO BID | 5/2,000 mg/day |

| Drug Name | Dosing Regimen | Maximum Dose |
|---|---|---|
| Jentadueto XR (linagliptin/metformin) | Individualized dose PO QD | 5/2,000 mg/day |
| Kombiglyze XR (saxagliptin/metformin) | Individualized dose PO QD | 5/2,000 mg/day |
| Onglyza (saxagliptin) | 2.5 or 5 mg PO QD | 5 mg/day |
| Qtern (saxagliptin/dapagliflozin) | One 5/5 mg tablet PO QD | 5/10 mg/day |
| Qternmet XR (saxagliptin/dapagliflozin/metformin) | Individualized dose PO QD | 5/10/2,000 mg/day |
| Steglujan (sitagliptin/ertugliflozin) | One 100/5 mg tablet PO QD | 100/15 mg/day |
| Tradjenta (linagliptin) | 5 mg PO QD | 5 mg/day |
| Trijardy XR (linagliptin/empagliflozin /metformin) | Individualized dose PO QD | 5/25/2,000 mg/day |

## VI. Product Availability

| Drug Name | Availability |
|---|---|
| Glyxambi (linagliptin /empagliflozin) | Tablets: 5/10 mg, 5/25 mg |
| Janumet (sitagliptin/metformin) | Tablets: 50/500 mg, 50/1,000 mg |
| Janumet XR (sitagliptin/metformin) | Tablets: 100/1,000 mg, 50/500 mg, 50/1,000 mg |
| Januvia (sitagliptin) | Tablets: 25 mg, 50 mg, 100 mg |
| Jentadueto (linagliptin/metformin) | Tablets: 2.5/500 mg, 2.5/850 mg, 2.5/1,000 mg |
| Jentadueto XR (linagliptin/metformin) | Tablets: 5/1,000 mg, 2.5/1,000 mg |
| Kombiglyze XR (saxagliptin/metformin) | Tablets: 5/500 mg, 5/1,000 mg, 2.5/1,000 mg |
| Onglyza (saxagliptin) | Tablets: 2.5 mg, 5 mg |
| Qtern (saxagliptin/dapagliflozin) | Tablet: 5/5 mg, 5/10 mg |
| Qternmet XR (saxagliptin/dapagliflozin/metformin) | Tablets: 2.5/2.5/1,000 mg, 2.5/5/1,000 mg, 5/5/1000 mg, 5/10/1,000 mg |
| Steglujan (sitagliptin/ertugliflozin) | Tablets: 100/5 mg, 100/15 mg |
| Tradjenta (linagliptin) | Tablets: 5 mg |
| Trijardy XR (linagliptin/empagliflozin /metformin) | Tablets: 2.5/5/1,000 mg, 5/10/1,000 mg, 2.5/12.5/1,000 mg, 5/25/1,000 mg |

## VII. References

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| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| 1Q 2019 Policy created per SDC recommendation based on previously approved clinical guidance: adapted from previously corporate approved policy CP.PST.18; modified to reflect that all DPP-4 inhibitors now require PA (instead of ST), added diagnosis, and added re-direction to Steglatro/Segluromet for Glyxambi per SDC; specified preferred DPP-4 inhibitors as alogliptin-containing products; modified minimum A1c related for concurrent use of metformin from 9% to 8.5% based on 2019 ADA guidelines. | 10.17.18 | 02.19 |
| Removed alogliptin-containing products from policy since they no longer require PA per SDC. | 02.07.19 | |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| Added Qtern, Qternmet XR, and Steglujan with re-direction to the preferred SGLT2 inhibitor Steglatro/Segluromet. | 05.08.19 | |
| 1Q 2020 annual review: no significant changes; added Trijardy XR with re-direction to Steglatro or Segluromet per SDC; references reviewed and updated. | 10.29.19 | 02.20 |
| Allowed bypass of Steglatro/Segluromet for patients with established cardiovascular disease/risk factors or diabetic nephropathy requesting a dapagliflozin- or empagliflozin-containing product per previously approved clinical guidance and SDC clarification. | 04.14.20 | |

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible

for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

**Note: For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.