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

Reference Number: CP.PMN.03
Effective Date: 09.19.18
Last Review Date: 02.25
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/metformin (Jentadueto®, Jentadueto® XR), saxagliptin (Onglyza®), saxagliptin/metformin (Kombiglyze® XR), sitagliptin (Brynovin™, Januvia®, Zituvio™), and sitagliptin/metformin (Janumet®, Janumet® XR, Zituvimet™, Zituvimet™ XR).

**If request is for a combination DPP-4 inhibitor and sodium glucose co-transporter 2 (SGLT2) inhibitor (e.g., linagliptin/empagliflozin [Glyxambi®], linagliptin/empagliflozin/metformin [Trijardy™ XR], saxagliptin/dapagliflozin [Qtern®], sitagliptin/ertugliflozin [Steglujan™]), refer to CP.PMN.14 SGLT2 Inhibitors.*

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.

Limitation(s) of use:

- DPP-4 inhibitors should not be used in patients with type 1 diabetes.
- Onglyza and Kombiglyze should not be used for the treatment of diabetic ketoacidosis.
- Brynovin, Januvia, Janumet, Janumet XR, Jentadueto, Jentadueto XR, Tradjenta, Zituvimet, Zituvimet XR, and Zituvio have not been studied in patients with a history of pancreatitis.

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. For antidiabetic medication-naïve members, requested agent is approvable if intended for concurrent use with metformin due to HbA1c ≥ 8.5% (drawn within the past 3 months);

4. One of the following (a or b):
   a. Request is for Brynovin, and member is unable to swallow tablets;
   b. All of the following (i, ii, and iii):
      i. Failure of ≥ 3 consecutive months of an alogliptin-containing product (e.g., alogliptin [Nesina®], alogliptin/metformin [Kazano®], alogliptin/pioglitazone [Oseni®]), unless clinically significant adverse effects are experienced or all are contraindicated;
      ii. Failure of ≥ 3 consecutive months of a saxagliptin-containing product (*generic saxagliptin and generic saxagliptin/metformin are preferred*), unless clinically significant adverse effects are experienced or all are contraindicated;
      iii. Failure of ≥ 3 consecutive months of a sitagliptin-containing product (*sitagliptin [Zituvio authorized generic] and sitagliptin/metformin [Zituvimet authorized generic] are preferred*), unless clinically significant adverse effects are experienced or all are contraindicated;
5. If request is for brand Onglyza or Kombiglyze XR, member must use generic saxagliptin or saxagliptin/metformin, unless contraindicated or clinically significant adverse effects are experienced;
6. If request is for brand Januvia/Zituvio or Janumet/Janumet XR/Zituvimet/Zituvimet XR, member must use sitagliptin (Zituvio authorized generic) or sitagliptin/metformin (Zituvimet authorized generic), unless contraindicated or clinically significant adverse effects are experienced;
7. 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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Type 2 Diabetes Mellitus (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;

b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*

2. Member is responding positively to therapy;
3. If request is for brand Onglyza or Kombiglyze XR, member must use generic saxagliptin or saxagliptin/metformin, unless contraindicated or clinically significant adverse effects are experienced;
4. If request is for brand Januvia/Zituvio or Janumet/Janumet XR/Zituvimet/Zituvimet XR, member must use sitagliptin (Zituvio authorized generic) or sitagliptin/metformin (Zituvimet authorized generic), unless contraindicated or clinically significant adverse effects are experienced;
5. 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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: 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 Extended-release: • Fortamet, Glumetza: 1,000 mg PO QD; increase as needed in increments of 500 mg/week • Glucophage XR: 500 mg PO QD; increase as needed in increments of 500 mg/week	Regular-release: 2,550 mg/day Extended-release: 2,000 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 only*) or moderate to severe renal impairment (*Qtern and Qternmet XR only*)
  - Acute or chronic metabolic acidosis, including diabetic ketoacidosis (*metformin-containing products only*)
- Boxed warning(s): lactic acidosis (*metformin-containing products only*)

Appendix D: General Information
- Per the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) guidelines:
  - Metformin is recommended for all patients with type 2 diabetes. It is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death. 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, 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. According to the ADA, a

reasonable HbA1c target for many non-pregnant adults is < 7% (≤ 6.5% per the AACE/ACE).
    - Starting with combination therapy with insulin may be considered for patients with baseline HbA1c > 10% or if symptoms of hyperglycemia are present.
- 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 therapy with insulin should be initiated. Each non-insulin agent added to initial therapy can lower HbA1c by 0.7-1%.

V. Dosage and Administration

Drug Name	Dosing Regimen	Maximum Dose
Brynovin (sitagliptin)	100 mg (4 mL) PO QD	100 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
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
Tradjenta (linagliptin)	5 mg PO QD	5 mg/day
Zituvimet (sitagliptin/metformin)	Individualized dose PO BID	100/2,000 mg/day
Zituvimet XR (sitagliptin/metformin)	Individualized dose PO QD	100/2,000 mg/day
Zituvio (sitagliptin)	100 mg PO QD	100 mg/day

VI. Product Availability

Drug Name	Availability
Brynovin (sitagliptin)	Oral solution: 25 mg/mL
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
Tradjenta (linagliptin)	Tablets: 5 mg
Zituvimet (sitagliptin/metformin)	Tablets: 50/500 mg, 50/1,000 mg
Zituvimet XR (sitagliptin/metformin)	Tablets: 50/500 mg, 50/1,000 mg, 100/1,000 mg
Zituvio (sitagliptin)	Tablets: 25 mg, 50 mg, 100 mg

VII. References

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2021 annual review: removed criteria for combination DPP4/SGLT2 products and directed requests to the SGLT2 policy instead; references reviewed and updated.	10.27.20	02.21

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2022 annual review: no significant changes; references reviewed and updated.	09.16.21	02.22
Template changes applied to other diagnoses/indications and continued therapy section.	09.19.22	
1Q 2023 annual review: no significant changes; references reviewed and updated.	10.26.22	02.23
RT4: added newly approved Zituvio to criteria.	11.08.23	
1Q 2024 annual review: RT4: added newly approved Zituvimet to criteria; references reviewed and updated. Per December SDC, added redirection to a saxagliptin-containing product, indicating generic is preferred; for Onglyza or Kombiglyze XR added requirement that member must use generic products.	12.06.23	02.24
RT4: added newly approved Zituvimet XR to criteria.	08.07.24	
Per September SDC, added redirection to sitagliptin-containing products, indicating authorized generics are preferred.	09.25.24	11.24
1Q 2025 annual review: no significant changes; references reviewed and updated.	11.06.24	02.25
RT4: added newly approved Brynovin to criteria.	01.23.25	

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.