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

Reference Number: CP.PMN.03
Effective Date: 09.19.18
Last Review Date: 02.21
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 (Januvia®), and sitagliptin/metformin (Janumet®, Janumet® 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®], saxagliptin/dapagliflozin/metformin [Qternmet® XR], sitagliptin/ertugliflozin [Steglujan™]), refer to CP.PMN.14 SGLT 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 or for the treatment of diabetic ketoacidosis.
- DPP-4 inhibitors 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 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. 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;
5. 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 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*) or moderate to severe renal impairment (*Qtern and Qternmet XR*)
  - 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 2020 American Diabetes Association (ADA) and American Association of Clinical Endocrinologists and 2020 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, 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 therapy with insulin may be considered for patients with baseline HbA1c > 10% 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 therapy with insulin 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
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

VI. Product Availability

Drug Name	Availability
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

VII. References

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10. Garber AJ, Duncan TG, Goodman AM, et al. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. Am J Med. 1997; 102: 491-497.
11. 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.

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	
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-	04.14.20	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
containing product per previously approved clinical guidance and SDC clarification.		
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

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.