Clinical Policy: Dipeptidyl Peptidase-4 (DPP-4) Inhibitors
Reference Number: CP.PPA.##
Effective Date: 09/17
Last Review Date: 08/17 Revision Log
Line of Business: Medicaid

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

Description
The following are dipeptidyl peptidase-4 (DPP-4) inhibitors requiring prior authorization: *PDL*: alogliptin (Nesina®), alogliptin/metformin (Kazano®), alogliptin/pioglitazone (Oseni®), linagliptin (Tradjenta®), linagliptin/metformin (Jentadueto®); *non-PDL*: linagliptin/empagliflozin (Glyxambi®), linagliptin/metformin (Jentadueto® XR), sitagliptin (Januvia®), sitagliptin/metformin (Janumet®, Janumet® XR), saxagliptin (Onglyza®), and saxagliptin/metformin (Kombiglyze® XR).

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

Limitations 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 (which may include office chart notes and lab results) 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. Member meets one of the following (a or b):
   a. Failure of ≥ 3 consecutive months of metformin at doses ≥ 2000 mg/day unless contraindicated or clinically significant adverse effects are experienced;
   b. Both (i and ii):
      i. HbA1c drawn within the past 3 months is > 7%;
      ii. Failure of ≥ 3 consecutive months of metformin at doses ≥ 1500 mg/day unless contraindicated or clinically significant adverse effects are experienced;
3. If request is for a non-PDL DPP-4 inhibitor, failure of ≥ 3 consecutive months of a PDL DPP-4 inhibitor at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced;

4. Dose does not exceed the FDA approved maximum recommended dose.

Approval duration: 12 months

B. Other diagnoses/indications

1. Refer to CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

Authorization is automatically renewed if there is a claims history of ≥ 90 day supply of the requested agent in the last 120 days

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

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. If request is for a dose increase, new dose does not exceed the FDA approved maximum recommended dose.

Approval duration: 12 months

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

1. Currently receiving medication via health plan benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized)

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 policy – CP.PMN.53 or evidence of coverage documents

B. Type 1 diabetes mellitus

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
PDL: preferred drug list
SGLT2: sodium-glucose co transporter 2

Appendix B: 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 2000 mg. However, the difference in adjusted mean change in HbA1c between the 1500 and 2000 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 American Diabetes Association (ADA) and American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) 2017 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 ≥ 9% per the ADA (≥ 7.5% 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% 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 0.9-1.1%.

V. Dosage and Administration

Drug	Dosing Regimen	Maximum Dose
PDL		
Jentadueto (linagliptin/metformin)	Individualized dose twice daily	5/2000 mg/day
Kazano (alogliptin/metformin)	Individualized dose twice daily	25/2000 mg/day
Nesina (alogliptin)	25 mg once daily	25 mg/day
Oseni (alogliptin/pioglitazone)	Individualized dose once daily	25/45 mg/day
Tradjenta (linagliptin)	5 mg once daily	5 mg/day
Non-PDL		
Glyxambi (linagliptin/empagliflozin)	5/10 mg once daily	5/25 mg/day
Janumet (sitagliptin/metformin)	Individualized dose once daily	100/2000 mg/day
Janumet XR (sitagliptin/metformin)	Individualized dose twice daily	100/2000 mg/day
Januvia (sitagliptin)	100 mg once daily	100 mg/day
Jentadueto XR (linagliptin/metformin)	Individualized dose once daily	5/2000 mg/day
Kombiglyze XR (saxagliptin/metformin)	Individualized dose once daily	5/2000 mg/day
Onglyza (saxagliptin)	2.5 or 5 mg once daily	5 mg/day

VI. Product Availability

Drug	Availability
PDL	
Jentadueto (linagliptin/metformin)	Tablets: 2.5/500 mg, 2.5/850 mg, 2.5/1000 mg
Kazano (alogliptin/metformin)	Tablets: 12.5/500 mg, 12.5/1000 mg

Nesina (alogliptin)	Tablets: 6.25 mg, 12.5 mg, 25 mg
Oseni (alogliptin/pioglitazone)	Tablets: 12.5/15 mg, 12.5/30 mg, 12.5/45 mg, 25/15 mg, 25/30 mg, 25/45 mg
Tradjenta (linagliptin)	Tablets: 5 mg
Non-PDL	
Glyxambi (linagliptin /empagliflozin)	Tablets: 5/10 mg, 5/25 mg
Janumet (sitagliptin/metformin)	Tablets: 50/500 mg, 50/1000 mg
Janumet XR (sitagliptin/metformin)	Tablets: 100/1000 mg, 50/500 mg, 50/1000 mg
Januvia (sitagliptin)	Tablets: 25 mg, 50 mg, 100 mg
Jentadueto XR (linagliptin/metformin)	Tablets: 5/1000 mg, 2.5/1000 mg
Kombiglyze XR (saxagliptin/metformin)	Tablets: 5/500 mg, 5/1000 mg, 2.5/1000 mg
Onglyza (saxagliptin)	Tablets: 2.5 mg, 5 mg

VII. References

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15. Garber AJ, Abrahamson MJ, Barzilay, JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2017 executive summary. Endocr Pract. 2017; 23(2): 207-238.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	04/17	08/17

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.