

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

Reference Number: CP.PST.18

Effective Date: 03.01.18

Last Review Date: 02.18

Line of Business: Health Insurance Marketplace, Medicaid

[Revision Log](#)

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: alogliptin (Nesina<sup>®</sup>), alogliptin/metformin (Kazano<sup>®</sup>), alogliptin/pioglitazone (Oseni<sup>®</sup>), linagliptin (Tradjenta<sup>®</sup>), linagliptin/empagliflozin (Glyxambi<sup>®</sup>), linagliptin/metformin (Jentadueto<sup>®</sup>, Jentadueto<sup>®</sup> XR), saxagliptin (Onglyza<sup>®</sup>), saxagliptin/metformin (Kombiglyze<sup>®</sup> XR), sitagliptin (Januvia<sup>®</sup>), and sitagliptin/metformin (Janumet<sup>®</sup>, Janumet<sup>®</sup> XR). Formulary status and requirement for step therapy vary by line of business.

### **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 (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<sup>®</sup> that DPP-4 inhibitors are **medically necessary** when the following criteria are met:

#### **I. Initial Approval Criteria**

##### **A. Electronic Step Therapy for DPP-4 Inhibitors (must meet all):**

1. Age  $\geq$  18 years;
2. Previous use of  $\geq$  3 consecutive months of metformin, unless contraindicated or clinically significant adverse effects are experienced;
3. If request is for a non-preferred DPP-4 inhibitor, member meets one of the following (a or b):
  - a. For Glyxambi: Previous use of  $\geq$  3 consecutive months of a preferred DPP-4 inhibitor OR a preferred sodium-glucose co-transporter 2 (SGLT2) inhibitor, unless all are contraindicated or clinically significant adverse effects are experienced;

- b. For all other non-preferred DPP-4 inhibitors: Previous use of  $\geq 3$  consecutive months of a preferred DPP-4 inhibitor, 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:** Not applicable

**II. Continued Therapy**

**A. Electronic Step Therapy for DPP-4 Inhibitors** (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:** Not applicable

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

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

AACE: American Association of Clinical Endocrinologists	FDA: Food and Drug Administration
ACE: American College of Endocrinology	GLP-1: glucagon-like peptide-1
ADA: American Diabetes Association	HbA1c: glycated hemoglobin
DPP-4: dipeptidyl peptidase-4	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.*

<b>Drug Name</b>	<b>Dosing Regimen</b>	<b>Dose Limit/ Maximum Dose</b>
metformin (Fortamet <sup>®</sup> , Glucophage <sup>®</sup> , Glucophage <sup>®</sup> XR, Glumetza <sup>®</sup> )	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: <ul style="list-style-type: none"> <li>• Fortamet, Glumetza: 1000 mg PO QD; increase as needed in increments of 500 mg/week</li> <li>• Glucophage XR: 500 mg PO QD; increase as needed in increments of 500 mg/week</li> </ul>	Regular-release: 2550 mg/day  Extended-release <ul style="list-style-type: none"> <li>• Fortamet: 2500 mg/day</li> <li>• Glucophage XR, Glumetza: 2000 mg/day</li> </ul>

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: 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 (AAACE/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, 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 AAACE/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 AAACE/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**

<b>Drug Name</b>	<b>Dosing Regimen</b>	<b>Maximum Dose</b>
Glyxambi (linagliptin/empagliflozin)	5/10 mg PO once daily	5/25 mg/day
Janumet (sitagliptin/metformin)	Individualized dose PO twice daily	100/2000 mg/day
Janumet XR (sitagliptin/metformin)	Individualized dose PO once daily	100/2000 mg/day
Januvia (sitagliptin)	100 mg PO once daily	100 mg/day
Jentadueto (linagliptin/metformin)	Individualized dose PO twice daily	5/2000 mg/day
Jentadueto XR (linagliptin/metformin)	Individualized dose PO once daily	5/2000 mg/day
Kazano (alogliptin/metformin)	Individualized dose PO twice daily	25/2000 mg/day
Kombiglyze XR (saxagliptin/metformin)	Individualized dose PO once daily	5/2000 mg/day
Nesina (alogliptin)	25 mg PO once daily	25 mg/day
Onglyza (saxagliptin)	2.5 or 5 mg PO once daily	5 mg/day

Drug Name	Dosing Regimen	Maximum Dose
Oseni (alogliptin/pioglitazone)	Individualized dose PO once daily	25/45 mg/day
Tradjenta (linagliptin)	5 mg PO once daily	5 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, 50/1000 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 (linagliptin/metformin)	Tablets: 2.5/500 mg, 2.5/850 mg, 2.5/1000 mg
Jentadueto XR (linagliptin/metformin)	Tablets: 5/1000 mg, 2.5/1000 mg
Kazano (alogliptin/metformin)	Tablets: 12.5/500 mg, 12.5/1000 mg
Kombiglyze XR (saxagliptin/metformin)	Tablets: 5/500 mg, 5/1000 mg, 2.5/1000 mg
Nesina (alogliptin)	Tablets: 6.25 mg, 12.5 mg, 25 mg
Onglyza (saxagliptin)	Tablets: 2.5 mg, 5 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

## VII. References

1. American Diabetes Association. Standards of medical care in diabetes—2017. *Diabetes Care*. 2017; 40(suppl 1): S1-S135.
2. Glyxambi Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; August 2017. Available at: [www.glyxambi.com](http://www.glyxambi.com). Accessed November 29, 2017.
3. Janumet Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; August 2017. Available at: [www.janumet.com](http://www.janumet.com). Accessed November 29, 2017.
4. Janumet XR Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; August 2017. Available at: [www.janumetxr.com](http://www.janumetxr.com). Accessed November 29, 2017.
5. Januvia Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; August 2017. Available at: [www.januvia.com](http://www.januvia.com). Accessed November 29, 2017.
6. Jentadueto Prescribing Information Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; August 2017. Available at: [www.jentadueto.com](http://www.jentadueto.com). Accessed November 29, 2017.
7. Jentadueto XR Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; August 2017. Available at: [www.jentaduetoxr.com](http://www.jentaduetoxr.com). Accessed November 29, 2017.
8. Kazano Prescribing Information. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; February 2017. Available at: [www.nesinafamily.com](http://www.nesinafamily.com). Accessed November 29, 2017.

9. Kombiglyze XR Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; February 2017. Available at: [www.kombiglyzexr.com](http://www.kombiglyzexr.com). Accessed November 29, 2017.
10. Nesina Prescribing Information. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; December 2016. Available at: [www.nesinafamily.com](http://www.nesinafamily.com). Accessed November 29, 2017.
11. Onglyza Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; February 2017. Available at: [www.onglyza.com](http://www.onglyza.com). Accessed November 29, 2017.
12. Oseni Prescribing Information. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; December 2016. Available at: [www.nesinafamily.com](http://www.nesinafamily.com). Accessed November 29, 2017.
13. Tradjenta Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; August 2017. Available at: [www.tradjenta.com](http://www.tradjenta.com). Accessed November 29, 2017.
14. 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.
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.	11.07.17	02.18

**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

## CLINICAL POLICY

### Dipeptidyl Peptidase-4 (DPP-4) Inhibitors



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.

**For Health Insurance Marketplace members**, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.

©2018 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene® and Centene Corporation® are registered trademarks exclusively owned by Centene Corporation.