

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

Reference Number: AZ.CP.PMN.43

Effective Date: 09.04.18

Last Review Date: 04.2020

Line of Business: Arizona 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 requiring prior authorization: alogliptin (Nesina[®]), alogliptin/metformin (Kazano[®]), alogliptin/pioglitazone (Oseni[®]), linagliptin (Tradjenta[®]), linagliptin/empagliflozin (Glyxambi[®]), linagliptin/metformin (Jentadueto[®], Jentadueto[®] XR), saxagliptin (Onglyza[®]), saxagliptin/metformin (Kombiglyze[®] XR), sitagliptin (Januvia[®]), ertugliflozin/sitagliptin (Steglujan[®]), sitagliptin/metformin (Janumet[®], Janumet[®] XR), dapagliflozin/saxagliptin (Qtern[®]), and dapagliflozin/saxagliptin/metformin (Qternmet[®] XR), empagliflozin/ linagliptin/ metformin (Trijardy[™] XR).

AHCCCS preferred drugs in this class include Januvia (sitagliptin), Janumet (sitagliptin/metformin), Janumet XR (sitagliptin/metformin extended-release), Jentadueto (linagliptin/metformin), Glyxambi (empagliflozin/linagliptin), Kombiglyze XR (saxagliptin/metformin extended-release), Onglyza (saxagliptin), and Tradjenta (linagliptin).

AHCCCS non-preferred drugs in this class include Nesina (alogliptin), Kazano (alogliptin/metformin), Oseni (alogliptin/pioglitazone), Jentadueto XR (linagliptin/metformin extended-release), Qtern (dapagliflozin/saxagliptin), Qternmet XR (dapagliflozin/saxagliptin/metformin) and Steglujan (ertugliflozin/sitagliptin), Trijardy[™] XR. (empagliflozin/ linagliptin/ metformin).

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 (including such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of Arizona Complete Health 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 \geq 18 years;
3. Member meets one of the following (a or b):
 - a. Failure of \geq 3 consecutive months of metformin at a minimum daily dose of 1500mg, unless contraindicated or clinically significant adverse effects are experienced;
 - b. HbA1c drawn within the past 3 months is \geq 8.5%, and concurrent use of metformin at a minimum daily dose of 1500mg, unless contraindicated or clinically significant adverse effects are experienced;
4. Request meets one of the following (a, b, or c):
 - a. Request is for a preferred DPP-4 inhibitor;
 - b. Request is for a non-preferred DPP-4 inhibitor: failure of \geq 3 consecutive months of all preferred DPP-4 inhibitors, unless contraindicated or clinically significant adverse effects are experienced;
 - c. Request is for a non-preferred DPP-4 inhibitor/SGLT-2 inhibitor combination therapy: failure of Glyxambi (empagliflozin/linagliptin);
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): AZ.CP.PMN.53 for Arizona 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. Request meets one of the following (a, b, or c):
 - a. Request is for a preferred DPP-4 inhibitor;
 - b. Request is for a non-preferred DPP-4 inhibitor: history of failure of \geq 3 consecutive months of all preferred DPP-4 inhibitors, unless contraindicated or clinically significant adverse effects are experienced;
 - c. Request is for a non-preferred DPP-4 inhibitor/SGLT-2 inhibitor combination therapy: history of failure of Glyxambi (empagliflozin/linagliptin);
3. Member is responding positively to therapy;
4. Documentation of continued metformin therapy (unless contraindicated);
5. If request is for a dose increase, the 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): AZ.CP.PMN.53 for Arizona 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 – AZ.CP.PMN.53 for Arizona Medicaid.

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: <ul style="list-style-type: none"> • 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: 2550 mg/day Extended-release: <ul style="list-style-type: none"> • Fortamet: 2500 mg/day • Glucophage XR: 2000 mg/day |
| Glyxambi (empagliflozin/linagliptin) | Initial, empagliflozin 10 mg/linagliptin 5 mg PO QD, may increase to empagliflozin 25 mg/linagliptin 5 mg PO QD | Empagliflozin 25 mg/linagliptin 5 mg |
| Januvia (sitagliptin) | 100 mg PO once daily | 100 mg/day |
| Janumet | Initial, sitagliptin 50 mg/metformin 500 | Sitagliptin 100 |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| (sitagliptin/metformin) | mg PO BID, may increase to sitagliptin 50 mg/metformin 1000 mg PO BID | mg/metformin 2000 mg |
| Janumet XR (sitagliptin/metformin extended-release) | Sitagliptin 100 mg/metformin 1000 mg PO QD | Sitagliptin 100 mg/metformin 2000 mg |
| Jentadueto (linagliptin/metformin) | Linagliptin 2.5 mg/metformin 500 mg PO BID with meals | Linagliptin 5 mg/ metformin 2,000 mg |
| Kombiglyze XR (saxagliptin/metformin extended-release) | Metformin 500 mg/ saxagliptin 5 mg PO QD | Metformin 2,000 mg/saxagliptin 5 mg |
| Onglyza (saxagliptin) | Initial, 2.5 to 5 mg PO QD | 5 mg/day |
| Tradjenta (linagliptin) | Initial, 5 mg PO QD | 5 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*)
 - End-stage renal disease or dialysis (*Glyxambi only*)
 - Metabolic acidosis, including diabetic ketoacidosis (*metformin-containing products only*)
 - NYHA Class III or IV heart failure (*Oseni only*)
- Boxed warning(s): lactic acidosis (*metformin-containing products only*), congestive heart failure (*Oseni 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 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 2019 American Diabetes Association (ADA) and American Association of Clinical Endocrinologists and 2017 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 \geq 1.5% above their target per the ADA (\geq 7.5% per the AACE/ACE). According to the ADA, a reasonable HbA1c target for many non-pregnant adults is < 7%.

CLINICAL POLICY

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors



- Starting with combination injectable therapy (i.e., with GLP-1 receptor agonist or insulin) may be considered for patients with baseline HbA1c $\geq 10\%$ or $\geq 2\%$ above their target per the ADA ($\geq 9\%$ 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%.

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 | 100/2000 mg/day |
| Janumet XR (sitagliptin/metformin) | Individualized dose PO QD | 100/2000 mg/day |
| Januvia (sitagliptin) | 100 mg PO QD | 100 mg/day |
| Jentadueto (linagliptin/metformin) | Individualized dose PO BID | 5/2000 mg/day |
| Jentadueto XR (linagliptin/metformin) | Individualized dose PO QD | 5/2000 mg/day |
| Kazano (alogliptin/metformin) | Individualized dose PO BID | 25/2000 mg/day |
| Kombiglyze XR (saxagliptin/metformin) | Individualized dose PO QD | 5/2000 mg/day |
| Nesina (alogliptin) | 25 mg PO QD | 25 mg/day |
| Onglyza (saxagliptin) | 2.5 or 5 mg PO QD | 5 mg/day |
| Oseni (alogliptin/pioglitazone) | Individualized dose PO QD | 25/45 mg/day |
| Tradjenta (linagliptin) | 5 mg PO QD | 5 mg/day |
| Trijardy XR (empagliflozin/linagliptin/ metformin) | 1 tablet PO QD | 25/5/1000 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 |

| Drug Name | Availability |
|--|-----------------------|
| Tradjenta (linagliptin) | Tablets: 5 mg |
| Trijardy XR (empagliflozin/ linagliptin/ metformin) | Tablets: 25/5/1000 mg |

VII. References

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| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|----------|-------------------|
| Policy created: adapted from previously corporate approved policy CP.PST.18 | 09.11.18 | 11.18 |
| Added AHCCCS non-preferred drugs; added metformin minimum daily doses; modified minimum A1c related for concurrent use of metformin from 9% to 8.5% based on 2019 ADA guidelines; Added requirement for a non-preferred DPP-4 inhibitor/SGLT-2 inhibitor combination therapy: failure of Glyxambi (empagliflozin/linagliptin); Added requirement for documentation of continued metformin therapy (unless contraindicated); | 03.22.19 | 04.19 |
| Added criterion for history of failure of preferred DPP-4 inhibitors for Continued Therapy; Added dosing regimen to Appendix B: Januvia, Janumet, Janumet XR, Jentadueto, Glyxambi, Kombiglyze XR, Onglyza, and Tradjenta. | 10.07.19 | 10.19 |
| 1Q 2020 annual review: no significant changes; references reviewed and updated. | 10.29.19 | 02.20 |
| 2Q 2020 added information and new drug reference for Trijardy™ XR. | 04.2020 | 04.2020 |

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.

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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.

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