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

Reference Number: IL.ERX.NPA.138
Effective Date: 06.01.21
Last Review Date: 05.21
Line of Business: Illinois 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: alogliptin (Nesina®), alogliptin/metformin (Kazano®), alogliptin/pioglitazone (Oseni®), 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 IL.ERX.NPA.136 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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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. Dose does not exceed the FDA approved maximum recommended dose (*see Section V*).

Approval duration: 12 months

B. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions 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 a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to ERX.PA.01 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 – ERX.PA.01 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 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

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*)
  - 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 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 2020 American Association of Clinical Endocrinologists and 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
Kazano (alogliptin/metformin)	Individualized dose PO BID	25/2,000 mg/day
Kombiglyze XR (saxagliptin/metformin)	Individualized dose PO QD	5/2,000 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

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
Kazano (alogliptin/metformin)	Tablets: 12.5/500 mg, 12.5/1,000 mg
Kombiglyze XR (saxagliptin/metformin)	Tablets: 5/500 mg, 5/1,000 mg, 2.5/1,000 mg
Nesina (alogliptin)	Tablets: 6.25 mg, 12.5 mg, 25 mg

Drug Name	Availability
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—2020. Diabetes Care. 2020; 43(suppl 1): S1-S212. Updated June 5, 2020. Accessed October 26, 2020.
2. Janumet Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; August 2019. Available at: www.janumet.com. Accessed October 27, 2020.
3. Janumet XR Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; August 2019. Available at: www.janumetxr.com. Accessed October 27, 2020.
4. Januvia Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; August 2019. Available at: www.januvia.com. Accessed October 27, 2020.
5. Jentadueto Prescribing Information Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; March 2020. Available at: www.jentadueto.com. Accessed October 27, 2020.
6. Jentadueto XR Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; March 2020. Available at: www.jentaduetoxr.com. Accessed October 27, 2020.
7. Kazano Prescribing Information. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; June 2019. Available at: www.nesinafamily.com. Accessed October 27, 2020.
8. Kombiglyze XR Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2019. Available at: www.kombiglyzexr.com. Accessed October 27, 2020.
9. Nesina Prescribing Information. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; June 2019. Available at: www.nesinafamily.com. Accessed October 27, 2020.
10. Onglyza Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2019. Available at: www.onglyza.com. Accessed October 27, 2020.
11. Oseni Prescribing Information. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; June 2019. Available at: www.nesinafamily.com. Accessed October 27, 2020.
12. Tradjenta Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; March 2020. Available at: www.tradjenta.com. Accessed October 27, 2020.
13. 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.
14. 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
Policy created	04.19.21	05.21

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.