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

Reference Number: HIM.PA.58
Effective Date: 03.01.18
Last Review Date: 02.19
Line of Business: HIM

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®) and linagliptin/empagliflozin (Glyxambi®).

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. HbA1c drawn within the past 3 months is ≥ 8.5%, and concurrent use of metformin unless contraindicated or clinically significant adverse effects are experienced;
4. If request is for Glyxambi, failure of ≥ 3 consecutive months of Steglatro™ or Segluromet™, unless both are contraindicated or clinically significant adverse effects are experienced;
5. If request is for Nesina, failure of ≥ 3 consecutive months of Tradjenta® or Januvia®, unless contraindicated or clinically significant adverse effects are experienced;
6. 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): HIM.PHAR.21 for health insurance marketplace.

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): HIM.PHAR.21 for health insurance marketplace.

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

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 – HIM.PHAR.21 for health insurance marketplace 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®,	Regular-release (Glucophage): 500 mg PO BID or 850 mg PO QD; increase as needed in	Regular-release: 2,550 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Glucophage® XR, Glumetza®)	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	Extended-release: • Fortamet: 2,500 mg/day • Glucophage XR, Glumetza: 2,000 mg/day
Tradjenta® (linagliptin)	5 mg PO QD	5 mg/day
Januvia® (sitagliptin)	100 mg PO QD	100 mg/day
Segluromet (ertugliflozin/ metformin)	Individualized dose PO BID	15/2,000 mg/day
Steglatro (ertugliflozin)	5 mg PO QD	15 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 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 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 ≥ 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%.
- Starting with combination injectable therapy (i.e., with GLP-1 receptor agonist or insulin) may be considered for patients with baseline HbA1c ≥ 10% or ≥ 2% above their target per the ADA (≥ 9% if symptoms are present per the AACE/ACE).

o 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
Nesina (alogliptin)	25 mg PO QD	25 mg/day

VI. Product Availability

Drug Name	Availability
Glyxambi (linagliptin/empagliflozin)	Tablets: 5/10 mg, 5/25 mg
Nesina (alogliptin)	Tablets: 6.25 mg, 12.5 mg, 25 mg

VII. References

1. American Diabetes Association. Standards of medical care in diabetes—2019. Diabetes Care. 2019; 42(suppl 1): S1-S193.
2. Glyxambi Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; October 2018. Available at: www.glyxambi.com. Accessed November 1, 2018.
3. Januvia Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; February 2018. Available at: www.januvia.com. Accessed November 1, 2018.
4. Nesina Prescribing Information. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; December 2016. Available at: www.nesinafamily.com. Accessed November 1, 2018.
5. Tradjenta Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; August 2017. Available at: www.tradjenta.com. Accessed November 1, 2018.
6. 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.
7. 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
Changed guideline to new format.	08.16	08.16
Added criteria for diagnosis of type 2 diabetes mellitus. Removed age restriction. Removed criteria regarding suboptimal glycemic control as failure of metformin would include suboptimal glycemic control. Added specific dose and duration for metformin trial. Added requirement for failure of a formulary DPP-4. Added max dosing criteria.	04.17	08.17
Added Tradjenta to policy. Added age restriction as safety and efficacy have not been established in pediatric populations. Added requirement that A1c in the last 3 months must be ≥ 6.5%. Removed requirement for failure of a formulary DPP-4 as all the agents in this guideline are on the formulary. Modified initial approval duration from 12 months to 6 months to allow for earlier assessment of therapeutic response. Added specific criteria surrounding required therapeutic response for re-auth.	08.18.17	11.17
Removed requirement for diagnosis Removed requirement for A1C submission Changed requirement for Metformin trial to be for 3 months without mandating a specific dose Allow first line use for members with A1C >= 9% References reviewed and updated Added requirement for Tradjenta trial prior to other agents.	11.07.17	02.18
Per SDC: added diagnosis. Per LOB director: Added alternative DPP4 Januvia as accepted trial as this agent no longer require PA.	10.17.18	
Removed Onglyza from criteria, does not require PA.	10.30.18	
1Q 2019 annual review: modified minimum A1c related for concurrent use of metformin from 9% to 8.5% based on 2019 ADA guidelines; references reviewed and updated.	11.01.18	02.19
Added requirement for trial of Steglatro or Segluromet prior to Glyxambi to align with criteria for Glyxambi in the SGLT2 clinical policy; members requesting other non-preferred DPP-4 inhibitors are still required to try/fail the preferred DPP-4 inhibitors Tradjenta and Januvia.	04.22.19	

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.

Note:
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 non-formulary policy; HIM.PA.103.