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

Reference Number: HIM.PA.58
Effective Date: 03.01.18
Last Review Date: 02.18
Line of Business: Health Insurance Marketplace 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 step therapy: alogliptin (Nesina®), linagliptin/empagliflozin (Glyxambi®), and sitagliptin (Januvia®).

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 health plans affiliated with Centene Corporation® that DPP-4 inhibitors are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Age ≥ 18 years;
2. Member meets one of the following (a or b):
   a. Previous use of ≥ 3 consecutive months of metformin, unless contraindicated or clinically significant adverse effects are experienced;
   b. HbA1c drawn within the past 3 months is ≥ 9%, and concurrent use of metformin unless contraindicated or clinically significant adverse effects are experienced;
3. Failure of ≥ 3 months trial of Tradjenta unless contraindicated on clinically significant adverse effect 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. 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
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: • Fortamet, Glumetza: 1000 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 • Fortamet: 2500 mg/day • Glucophage XR, Glumetza: 2000 mg/day
Tradjenta (linagliptin)	5 mg daily	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: 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 2018 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, 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 Name	Dosing Regimen	Maximum Dose
Glyxambi (linagliptin/empagliflozin)	5/10 mg PO once daily	5/25 mg/day
Januvia (sitagliptin)	100 mg PO once daily	100 mg/day
Nesina (alogliptin)	25 mg PO once daily	25 mg/day

VI. Product Availability

Drug Name	Availability
Glyxambi (linagliptin/empagliflozin)	Tablets: 5/10 mg, 5/25 mg
Januvia (sitagliptin)	Tablets: 25 mg, 50 mg, 100 mg
Nesina (alogliptin)	Tablets: 6.25 mg, 12.5 mg, 25 mg

VII. References

1. American Diabetes Association. Standards of medical care in diabetes—2018. Diabetes Care. 2018; 41(suppl 1): S1-S159.
2. Glyxambi Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; August 2017. Available at: www.glyxambi.com. Accessed November 29, 2017.
3. Januvia Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; August 2017. Available at: www.januvia.com. Accessed November 29, 2017.
4. Nesina Prescribing Information. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; December 2016. Available at: www.nesinafamily.com. Accessed November 29, 2017.
5. Onglyza Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; February 2017. Available at: www.onglyza.com. Accessed November 29, 2017.
6. Tradjenta Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; August 2017. Available at: www.tradjenta.com. Accessed November 29, 2017.
7. 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.

8. 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

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

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