Clinical Policy: Dipeptidyl Peptidase-4 (DPP-4) Inhibitors
Reference Number: AZ.CP.PHAR.26
Effective Date: 09.04.18
Last Review Date: 09.12.18
Line of Business: Arizona Medicaid

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®), and sitagliptin/metformin
(Janumet®, Janumet® XR).

AHCCCS preferred drugs in this class include Januvia, Janumet, Janumet XR, Jentadueto,
Tradjenta, Glyxambi, Onglyza and Kombigylze.

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. 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 ≥ 9%, and concurrent use of metformin
            unless contraindicated or clinically significant adverse effects are experienced;
      4. Request meets one of the following (a, or b):
A. Request is for a preferred DPP-4 inhibitor;
b. Request is for a non-preferred DPP-4 inhibitor: failure of ≥ 3 consecutive months of all preferred DPP-4 inhibitors, unless contraindicated or clinically significant adverse effects are experienced;
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): CP.PMN.53 for 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. 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): CP.PMN.53 for 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 – CP.PMN.53 for Medicaid 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.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
</table>
| 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: 500 or 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: 2000 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):
  o History of serious hypersensitivity reaction to the requested drug product
  o Severe renal impairment (metformin-containing products and Glyxambi)
  o End-stage renal disease or dialysis (Glyxambi only)
  o Metabolic acidosis, including diabetic ketoacidosis (metformin-containing products only)
  o 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 2018 American Diabetes Association (ADA) and American Association of Clinical Endocrinologists and 2017 American College of Endocrinology (AACE/ACE) guidelines:
  o 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 ≥ 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

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyxambi (linagliptin/empagliflozin)</td>
<td>5/10 mg PO QD</td>
<td>5/25 mg/day</td>
</tr>
<tr>
<td>Janumet (sitagliptin/metformin)</td>
<td>Individualized dose PO BID</td>
<td>100/2000 mg/day</td>
</tr>
<tr>
<td>Janumet XR (sitagliptin/metformin)</td>
<td>Individualized dose PO QD</td>
<td>100/2000 mg/day</td>
</tr>
<tr>
<td>Januvia (sitagliptin)</td>
<td>100 mg PO QD</td>
<td>100 mg/day</td>
</tr>
<tr>
<td>Jentadueto (linagliptin/metformin)</td>
<td>Individualized dose PO BID</td>
<td>5/2000 mg/day</td>
</tr>
<tr>
<td>Jentadueto XR (linagliptin/metformin)</td>
<td>Individualized dose PO QD</td>
<td>5/2000 mg/day</td>
</tr>
<tr>
<td>Kazano (alogliptin/metformin)</td>
<td>Individualized dose PO BID</td>
<td>25/2000 mg/day</td>
</tr>
<tr>
<td>Kombiglyze XR (saxagliptin/metformin)</td>
<td>Individualized dose PO QD</td>
<td>5/2000 mg/day</td>
</tr>
<tr>
<td>Nesina (alogliptin)</td>
<td>25 mg PO QD</td>
<td>25 mg/day</td>
</tr>
<tr>
<td>Onglyza (saxagliptin)</td>
<td>2.5 or 5 mg PO QD</td>
<td>5 mg/day</td>
</tr>
<tr>
<td>Oseni (alogliptin/pioglitazone)</td>
<td>Individualized dose PO QD</td>
<td>25/45 mg/day</td>
</tr>
<tr>
<td>Tradjenta (linagliptin)</td>
<td>5 mg PO QD</td>
<td>5 mg/day</td>
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VI. Product Availability

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Availability</th>
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<tr>
<td>Glyxambi (linagliptin/empagliflozin)</td>
<td>Tablets: 5/10 mg, 5/25 mg</td>
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<tr>
<td>Janumet (sitagliptin/metformin)</td>
<td>Tablets: 50/500 mg, 50/1000 mg</td>
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<tr>
<td>Janumet XR (sitagliptin/metformin)</td>
<td>Tablets: 100/1000 mg, 50/500 mg, 50/1000 mg</td>
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<td>Januvia (sitagliptin)</td>
<td>Tablets: 25 mg, 50 mg, 100 mg</td>
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<td>Jentadueto (linagliptin/metformin)</td>
<td>Tablets: 2.5/500 mg, 2.5/850 mg, 2.5/1000 mg</td>
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<tr>
<td>Jentadueto XR (linagliptin/metformin)</td>
<td>Tablets: 5/1000 mg, 2.5/1000 mg</td>
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<tr>
<td>Kazano (alogliptin/metformin)</td>
<td>Tablets: 12.5/500 mg, 12.5/1000 mg</td>
</tr>
<tr>
<td>Kombiglyze XR (saxagliptin/metformin)</td>
<td>Tablets: 5/500 mg, 5/1000 mg, 2.5/1000 mg</td>
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<tr>
<td>Nesina (alogliptin)</td>
<td>Tablets: 6.25 mg, 12.5 mg, 25 mg</td>
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<tr>
<td>Onglyza (saxagliptin)</td>
<td>Tablets: 2.5 mg, 5 mg</td>
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<tr>
<td>Oseni (alogliptin/pioglitazone)</td>
<td>Tablets: 12.5/15 mg, 12.5/30 mg, 12.5/45 mg, 25/15 mg, 25/30 mg, 25/45 mg</td>
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<tr>
<td>Tradjenta (linagliptin)</td>
<td>Tablets: 5 mg</td>
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VII. References


Reviews, Revisions, and Approvals

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<thead>
<tr>
<th>Policy created: adapted from previously corporate approved policy CP.PST.18</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
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<tr>
<td>09.11.18</td>
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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.

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CLINICAL POLICY
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

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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