Policy and Procedure	
PHARMACY STEP THERAPY POLICY AND CRITERIA ORPTCEND010.0425	**ENDOCRINE AND METABOLIC DRUGS** **DPP-4 INHIBITORS** See Table 1 for Medications
Effective Date: 7/1/2025	**Review/Revised Date**: 10/07, 06/08, 12/08, 04/09, 12/09, 02/10, 12/10, 02/11, 04/11, 06/12, 08/13, 04/14, 04/15, 03/16, 03/17, 03/18, 05/18, 01/19, 03/19, 02/20, 06/20, 10/20, 11/20, 03/21, 02/22, 02/23, 03/24. 05/24, 02/25 (KN)
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Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Commercial
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. One of the following:
    a. History of use of a generic dipeptidyl peptidase-4 (DPP-4) inhibitor (such as sitagliptin, saxagliptin, or alogliptin) within the previous 180 days (verified by pharmacy claims), or
    b. Documentation of trial, intolerance, or contraindication to a generic dipeptidyl peptidase-4 (DPP-4) inhibitor

EXCLUSION CRITERIA:
Concurrent use with another dipeptidyl peptidase-4 (DPP-4) inhibitor or a GIP/GLP-1 receptor agonist

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

PHARMACY STEP THERAPY POLICY AND CRITERIA ORPTCEND010	ENDOCRINE AND METABOLIC DRUGS DPP-4 INHIBITORS See Table 1 for Medications

QUANTITY LIMITATIONS:

One tablet per day: Glyxambi, Janumet XR, Januvia, Jentadueto XR 5 mg, Kombiglyze XR 5 mg, Onglyza, Qtern, Steglujan, Tradjenta, Trijardy XR 10 mg and 25 mg, Zituvio
Two tablets per day: Janumet, Jentadueto, Jentadueto XR 2.5 mg, Kombiglyze XR 2.5 mg, Trijardy XR 5 mg and 12.5 mg

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Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Dipeptidyl peptidase-4 (DPP-4) inhibitors inhibit the dipeptidyl peptidase-4 enzyme responsible for rapid degradation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP). These hormones are released throughout the day but are increased after meals; both stimulate glucose dependent insulin release from pancreatic beta-cells. GLP-1 decreases glucose-dependent glucagon release from pancreatic alpha-cells leading to suppression of endogenous glucose production and delaying gastric emptying. The result of these actions is an increase of glucose uptake in cells and a decrease in glucose production in the liver, leading to reduction in blood glucose levels. The concurrent use of a DPP-4 inhibitor with a GLP-1 receptor agonist is not recommended due to the similar mechanism of actions between these two classes of medications.

FDA APPROVED INDICATIONS:

Table 1. DPP-4 Inhibitors applicable to this policy

Generic Name	Available Products	FDA Indication(s)

sitagliptin (SITA)	Janumet® (SITA/metformin) Janumet XR® (SITA/metformin) Januvia® (SITA) Steglujan® (SITA/ertugliflozin)	An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
saxagliptin (SAXA)	Kombiglyze XR® (SAXA/metformin) Qtern® (SAXA/dapagliflozin)	
linagliptin (LINA)	Tradjenta® (LINA) Jentadueto® (LINA/metformin) Jentadueto XR® (LINA/metformin) Trijardy XR® (empagliflozin/LINA/metformin)* Glyxambi® (empagliflozin/LINA)*	

*Policy criteria for these agents only applies for Medicaid (available without step therapy for Commercial). Additionally, empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease

POSITION STATEMENT:

Efficacy

DPP-4 inhibitors have shown modest efficacy (A1c reduction of ~0.6%) in clinical trials for patients with type 2 diabetes. A systemic review and meta-analysis by Mishriky et al. 2018 compared DPP-4 inhibitors to SGLT2 inhibitors as add-on therapy to metformin in patients with T2DM. Investigators searched for randomized trials that reported a change in HbA1C over time, excluding trials that only reported change in HbA1C from baseline to less than 12 weeks.

- Seven trials (n=2687) were found to meet inclusion criteria. For DPP-4 inhibitors: five trials investigated sitagliptin, one trial investigated linagliptin, and one trial investigated saxagliptin. For SGLT2 inhibitors: three trials investigated empagliflozin, two trials investigated canagliflozin, one trial investigated dapagliflozin, and one looked at ertugliflozin. Trials that measured outcome from baseline to 12 and 26 weeks were pooled together while trials that reported results at 52 weeks or longer were pooled together.
- Pooled results for change in HbA1C from baseline to 12 to 26 weeks: No significant difference was found between DPP-4 inhibitors and SGLT2 inhibitors. However, a statistically significant reduction was found between the two classes in pooled results of trials that measured change in HbA1C from baseline to 52 weeks or longer, favoring SGLT2 inhibitors over DPP-4 inhibitors (mean difference [95% CI] = −0.11% [−0.20, −0.03], I_2 = 0%).
- Pooled results for change in fasting plasma glucose showed a statistically significant reduction favoring SGLT2 inhibitors compared to DPP-4 inhibitors. The mean difference was −11.68 mg/dL (95% CI: −14.61 to −8.74) and I_2= 4% for the pooled results from the 12 to 26 weeks trials and −12.49 mg/dL 95% CI: −16.43 to −8.55), I_2= 0% for the pooled results from the 52 weeks or longer trials.

Safety

DPP-4 inhibitors are generally well tolerated with minimal side effects. The FDA now requires cardiovascular studies for anti-diabetic medications coming to market. These studies did not identify a benefit in terms of ASCVD risk reduction for any of the DPP-4 inhibitors; this class is considered to have a "neutral" effect for ASCVD risk reduction. However, there was a statistically significant safety signal in the saxagliptin clinical trial (SAVOR-TIMI 53) leading to a strong warning in the package labeling:

- The SAVOR-TIMI 53 trial enrolled and randomized patients (N=16,492) with type 2 diabetes and established cardiovascular disease, or with multiple risk factors for vascular disease, to receive saxagliptin daily or placebo.
    - The primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke. A key secondary endpoint was the primary composite end point plus hospitalization for heart failure, coronary revascularization, or unstable angina.
    - The results of the primary endpoint were not significant. A total of 613 (7.3%) saxagliptin patients and 609 (7.2%) placebo patients had an event (hazard ratio 1.00; 95% confidence interval [CI], 0.89 to 1.12; P<0.001 for non-inferiority).
    - The secondary endpoint showed a statistically significant increased risk of hospitalization for heart failure (3.5% vs. 2.8%; hazard ratio, 1.27; 95% CI, 1.07 to 1.51; P=0.007).

Sitagliptin, linagliptin and alogliptin were also found to be neutral in terms of ASCVD risk reduction and none of them exhibited a statistically significant increased risk of heart failure hospitalizations as seen in the saxagliptin trial. Alogliptin did have a numerically higher hospitalization rate, but was not considered significant. These agents all carry a precaution in labeling due to the results with saxagliptin, but it is not necessarily considered a class effect at this point.

Place in Therapy

The 2025 American Diabetes Association (ADA) Standards of Care recommend a patient-centered approach to guide the choice of pharmacologic agents. Patient's comorbidities (e.g., atherosclerotic cardiovascular disease, heart failure, chronic kidney disease), hypoglycemia risk, impact on weight, cost, risk for side effects, and preferences should be considered.

- For patients with established atherosclerotic cardiovascular disease (ASCVD) or at high risk for ASCVD [defined as patients ≥55 years of age with two of more additional risk (e.g. obesity, hypertension, smoking, dyslipidemia, or albuminuria)]:

  - A sodium–glucose cotransporter-2 (SGLT-2) inhibitor or glucagon-like peptide-1 receptor agonists (GLP-1 RAs) with demonstrated cardiovascular disease benefit should be initiated
- For patients with heart failure:
  - The recommendation is to add a SGLT-2 inhibitor with proven benefit in this population
- For patients with chronic kidney disease (CKD) and on maximally tolerated dose of and angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB):
  - The recommendation is to add a SGLT-2 inhibitor with proven benefit in reducing CKD progression
- For patients without these comorbidities and the goal is to achieve and maintain:
  - Glycemic control, the ADA continues to recommend metformin as the first-line treatment, or a combination of therapy that "provides adequate efficacy to achieve and maintain goals."
    - Very high efficacy: GLP-1 RAs such as dulaglutide, semaglutide, tirzepatide
    - High efficacy: metformin, SGLT2i, sulfonylurea, thiazolidinediones
    - Intermediate efficacy: DPP-4i
  - Weight management, the ADA recommends setting individualized goals. If medications are considered for addition, those with high efficacy in reducing glucose levels and weight should be considered
    - Very high efficacy: GLP-1 RAs such as semaglutide, tirzepatide
    - High efficacy: dulaglutide, liraglutide
    - Intermediate efficacy: SGLT2i
    - Neutral efficacy: DPP-4i, metformin

REFERENCE/RESOURCES:

1. Relevent and current package inserts
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4. Scirica BM, Bhatt DL, Braunwald E, et al; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369(14):1317-1326.
5. Zannad F, Cannon CP, Cushman WC, et al. Heart Failure and Mortality Outcomes in patients with Type 2 Diabetes taking alogliptin versus placebo in

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7. Rosenstock J, Perkovic V, Johansen OE, et al. Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. *JAMA*. 2019; 321(1);69-79
8. Rosenstock J, Kahn SE, Johansen OE, et al. Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes: The CAROLINA Randomized Clinical Trial. *JAMA*. 2019; doi: 10.1001/jama.2019.13772. [Epub ahead of print]