This program applies to Medicaid. It is implemented with auto-grandfathering.

Step Therapy only applies to the MN Medicaid Preferred Drug List (PDL) preferred drugs: Januvia, Janumet, Jentadueto, Kombiglyze XR, Onglyza, and Tradjenta

The BCBS MN Step Therapy Supplement applies to this program for Medicaid.

### FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Limitations for use</th>
<th>Dosage and Administration</th>
</tr>
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<tbody>
<tr>
<td><strong>DPP-4 Inhibitors</strong></td>
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</table>
| Januvia® (sitagliptin) tablet | Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus | • Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.  
• Has not been studied in patients with a history of pancreatitis. | 25 mg, 50 mg, 100 mg; 1 tablet per day, maximum daily dose of 100 mg |
| Nesina® (alogliptin) tablet | Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus | • Is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings. | 6.25 mg, 12.5 mg, 25 mg; 1 dose per day, maximum daily dose of 25 mg |
| Onglyza® (saxagliptin) tablet | Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus | • Is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings. | 2.5 mg, 5 mg; 1 dose per day, maximum daily dose of 5 mg |
| Tradjenta® (linagliptin) tablet | Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus | • Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.  
• Has not been studied in patients with a history of pancreatitis | 5 mg; 1 dose per day, maximum daily dose of 5 mg |
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<td><strong>DPP-4 Inhibitor Combinations</strong></td>
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</table>
| **Janumet®** (sitagliptin/metformin) tablet | Indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus | • Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.  
• Has not been studied in patients with a history of pancreatitis. | 50 mg/500 mg – 100 mg/1000 mg per day; two doses per day, maximum daily dose of 100 mg/2000 mg |
| **Janumet® XR** (sitagliptin/metformin extended-release) tablet | Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus | • Should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.  
• Has not been studied in patients with a history of pancreatitis. | 50 mg/500 mg, 50 mg /1000 mg, 100 mg/1000 mg; one dose per day, maximum daily dose of 100 mg/2000 mg |
| **Jentadueto®** (linagliptin/metformin) tablet | Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate | • Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.  
• Has not been studied in patients with a history of pancreatitis. | 2.5 mg/500 mg, 2.5 mg/850 mg, 2.5 mg/1000 mg; two doses per day, maximum daily dose of 5 mg/2000 mg |
| **Jentadueto XR®** (linagliptin/metformin extended release) tablet | Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate | • Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.  
• Has not been studied in patients with a history of pancreatitis. | 2.5 mg/1000 mg, 5 mg/2000 mg; one dose per day, maximum daily dose of 5 mg/2000 mg |
<p>| <strong>Kazano™</strong> (alogliptin/metformin) tablet | Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both alogliptin and metformin is appropriate | • Not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings. | 12.5 mg/500 mg, 12.5 mg/1000; two doses per day, maximum daily dose of 25 mg/2000 mg |</p>
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</table>
| **Kombiglyze XR™**
(saxagliptin/ metformin extended-release)
tablet | Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate. | • Not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. | 2.5 mg/1000 mg, 5 mg/500 mg, 5 mg/1000 mg; one dose per day, maximum daily dose of 5 mg/2000 mg |
| **Oseni™**
(alogliptin/ pioglitazone)
tablet | Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both alogliptin and pioglitazone is appropriate. | • Not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings. | 12.5 mg/15 mg, 12.5 mg/30 mg, 12.5 mg/45 mg, 25 mg/15 mg, 25 mg/30 mg, 25 mg/45 mg; one dose per day, maximum daily dose of 25 mg/45 mg |
CLINICAL RATIONALE
The American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) recommend metformin as the preferred first-line drug in type II diabetes mellitus.\textsuperscript{1,2} Two-drug combinations should be considered if metformin fails to achieve A1c target after approximately 3 months. The choice of the second agent (sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter 2 inhibitor, basal insulin, glucagon-like peptide 1 agonist) is based upon patient and drug characteristics, with the goal of improving glycemic control while minimizing side effects and patient burden.\textsuperscript{1}

For additional clinical information see the Prime Therapeutics Formulary Chapters 4.6H: Combination Antidiabetic Agents and 4.6K: Dipeptidyl Peptidase-4 (DPP-4) Inhibitors.

SAFETY
Jentadueto, Jentadueto XR, Kazano, and Kombiglyze XR carry a black box warning for lactic acidosis.

- Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin associated lactic acidosis was characterized by elevated blood lactate levels (> 5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/ml
- Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.
- Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high-risk groups are provided in the full prescribing information
- If metformin-associated lactic acidosis is suspected, immediately discontinue the medication and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.\textsuperscript{6,7,10,13}

Oseni carries a black box warning for congestive heart failure.

- Thiazolidinediones, including pioglitazone, cause or exacerbate congestive heart failure in some patients.
- After initiation of Oseni and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of pioglitazone in Oseni must be considered.
- OSENI is not recommended in patients with symptomatic heart failure. Initiation of Oseni in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated.\textsuperscript{11}

REFERENCES
DPP-4 Inhibitors and Combinations Step Therapy

TARGET AGENTS
- Januvia® (sitagliptin)
- Janumet® (sitagliptin/metformin)
- Jentadueto® (linagliptin/metformin)
- Kombiglyze XR™ (saxagliptin/metformin ER)
- Onglyza® (saxagliptin)
- Tradjenta® (linagliptin)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Target Agents will be approved when ONE of the following is met:
1. Information has been provided that indicates the patient is currently being treated with the requested agent within the past 90 days
   OR
2. The prescriber states the patient is currently being treated with the requested agent within the past 90 days AND is at risk if therapy is changed
   OR
3. The patient’s medication history includes use of an agent containing metformin, sulfonylurea, or insulin in the past 999 days
   OR
4. The prescriber has stated that the patient has tried insulin or an agent containing metformin or sulfonylurea AND ONE of the following:
   a. Insulin or an agent containing metformin or sulfonylurea was discontinued due to lack of effectiveness or an adverse event
      OR
   b. The prescriber has submitted an evidence-based and peer-reviewed clinical practice guideline supporting the use of the requested agent over insulin or an agent containing metformin or sulfonylurea
   OR
5. The patient has an intolerance or hypersensitivity to ONE of the following: sulfonylurea, metformin, or insulin
   OR
6. The patient has an FDA labeled contraindication to ALL of the following: sulfonylureas, metformin, and insulins
   OR
7. The prescriber has provided documentation that ALL of the following agents: metformin, sulfonylurea, and insulin cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm
   OR
8. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
      AND
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
      AND
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm
**Length of approval:** 12 months

**NOTE:** If Quantity Limit program also applies, please refer to Quantity Limit documents.