DPP-4 Inhibitors and Combinations Step Therapy with Quantity Limit Program Summary

This program applies to Medicaid.

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

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

POLICY REVIEW CYCLE

Effective Date	Date of Origin
06-01-2024	11-01-2018

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Janumet® (sitagliptin/metformin) Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Should not be used in patients with type 1 diabetes. • Has not been studied in patients with a history of pancreatitis		5
Janumet® XR (sitagliptin-metformin HCl Tab ER) Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Should not be used in patients with type 1 diabetes. • Has not been studied in patients with a history of pancreatitis		6
Januvia® (sitagliptin) Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Should not be used in patients with type 1 diabetes. • Has not been studied in patients with a history of pancreatitis.		1
Jentadueto® (linagliptin/metformin) Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Should not be used in patients with type 1 diabetes • Has not been studied in patients with a history of pancreatitis		7

Agent(s)	FDA Indication(s)	Notes	Ref#
Jentadueto XR® (linagliptin/metformin ER) Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Should not be used in patients with type 1 diabetes • Has not been studied in patients with a history of pancreatitis		8
Kazano™, Alogliptin/metformin Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Should not be used in patients with type 1 diabetes mellitus		10
Kombiglyze™ XR (saxagliptin/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 saxagliptin and metformin is appropriate Limitations of use: • Not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis	*- generic available	9
Nesina®, Alogliptin Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Should not be used in patients with type 1 diabetes mellitus		2
Onglyza® (saxagliptin)* Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Not used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis	*-generic available	3
Oseni®, Alogliptin/pioglitazone Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Should not be used in patients with type 1 diabetes		11
Tradjenta® (linagliptin) Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Should not be used in patients with type 1 diabetes, as it would not be effective in these settings		4

Agent(s)	FDA Indication(s)	Notes	Ref#
	• Has not been studied in patients with a history of pancreatitis		
Zituvio™ (sitagliptin) Tablet	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of Use: • Zituvio is not recommended in patients with type 1 diabetes mellitus • Zituvio has not been studied in patients with a history of pancreatitis		14

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Diabetes	The American Diabetes Association (ADA) states that first-line therapy depends on comorbidities, patient-centered treatment factors, and management needs and generally includes metformin and comprehensive lifestyle modification. Because type 2 diabetes is a progressive disease in many patients, maintenance of glycemic targets with monotherapy is often possible for only a few years, after which combination therapy is necessary. Traditional recommendations have been to use stepwise addition of medications to metformin to maintain A1C at target.(12,13) Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death. Metformin is available in an immediate-release form for twice-daily dosing or as an extended-release form that can be given once daily. Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, weight, and cardiovascular mortality.(13)
Safety	Janumet, Jentadueto, Jentadueto XR, Kazano, and Kombiglyze XR carry a black box warning for lactic acidosis:(7-10) • 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 (greater than 5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally greater than 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. Oseni carries a black box warning for congestive heart failure:(11) • 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. Janumet, Janumet XR, and Kombiglyze XR have the following contraindications:(5,6,9) • Severe renal impairment: (eGFR below 30 mL/min/1.73 m^2). • Metabolic acidosis, including diabetic ketoacidosis. • History of a serious hypersensitivity reaction (e.g., anaphylaxis, angioedema, exfoliative skin conditions) to the active ingredients, metformin, or any excipients. Jentadueto, Jentadueto XR, and Kazano have the following contraindications:(7,8,10) • Severe renal impairment (eGFR below 30 mL/min/1.73 m^2). • Metabolic acidosis, including diabetic ketoacidosis. • Hypersensitivity to the active ingredients or any of the excipients. Januvia, Nesina, Onglyza, and Tradjenta have the following contraindication:(1-4) • History of serious hypersensitivity to the active ingredient or any of the excipients. Oseni has the following contraindication:(11) • Serious hypersensitivity reaction to alogliptin or pioglitazone, components of Oseni, or any of the excipients. • Do not initiate Oseni in patients with established NYHA Class III or IV heart failure. Zituvio has the following contraindication:(14) • History of a serious hypersensitivity reaction to sitagliptin or any of the excipients in Zituvio, such as anaphylaxis or angioedema.

REFERENCES

Number	Reference
1	Januvia prescribing information. Merck & Co., Inc. July 2022.
2	Nesina prescribing information. Takeda Pharmaceuticals America, Inc. July 2023.
3	Onglyza prescribing information. Astra Zeneca. October 2019.
4	Tradjenta prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. June 2023.
5	Janumet prescribing information. Merck & Co., Inc. July 2022.
6	Janumet XR prescribing information. Merck & Co., Inc. July 2022.
7	Jentadueto prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. June 2023.
8	Jentadueto XR prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. June 2023.
9	Kombiglyze XR prescribing information. Bristol-Meyers Squibb Company/AstraZeneca Pharmaceuticals LP. October 2019.

Number	Reference
10	Kazano prescribing information. Takeda Pharmaceuticals America, Inc. July 2023.
11	Oseni prescribing information. Takeda Pharmaceuticals America, Inc. March 2022.
12	American Diabetes Association. Standards of Medical Care in Diabetes-2022. Available at https://diabetesjournals.org/care/issue/45/Supplement_1.
13	Nuha A. ElSayed, et. al, American Diabetes Association, 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2023. Diabetes Care 1 January 2023; 46 (Supplement_1): S140–S157. https://doi.org/10.2337/dc23-S009.
14	Zituvio prescribing information. Zydus Pharmaceuticals (USA) Inc. October 2023.

POLICY AGENT SUMMARY STEP THERAPY

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Janumet	sitagliptin-metformin hcl tab	50-1000 MG ; 50-500 MG	M ; N ; O	N		
Janumet xr	sitagliptin-metformin hcl tab er	100-1000 MG ; 50-1000 MG ; 50-500 MG	M ; N ; O	N		
Januvia	sitagliptin phosphate tab	100 MG ; 25 MG ; 50 MG	M ; N ; O	N		
Jentadueto	linagliptin-metformin hcl tab	2.5-1000 MG ; 2.5-500 MG ; 2.5-850 MG	M ; N ; O	N		
Jentadueto xr	linagliptin-metformin hcl tab er	2.5-1000 MG ; 5-1000 MG	M ; N ; O	N		
Kombiglyze xr	saxagliptin-metformin hcl tab er	2.5-1000 MG ; 5-1000 MG ; 5-500 MG	M ; N ; O	O ; Y		
Nesina	alogliptin benzoate tab	12.5 MG ; 25 MG ; 6.25 MG	M ; N ; O	M ; N		
Onglyza	saxagliptin hcl tab	2.5 MG ; 5 MG	M ; N ; O	O ; Y		
Tradjenta	linagliptin tab	5 MG	M ; N ; O	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Janumet	Sitagliptin-Metformin HCl Tab 50-1000 MG	50-1000 MG	60	Tablets	30	DAYS			
Janumet	Sitagliptin-Metformin HCl Tab 50-500 MG	50-500 MG	60	Tablets	30	DAYS			
Janumet xr	Sitagliptin-Metformin HCl Tab ER 24HR 100-1000 MG	100-1000 MG	30	Tablets	30	DAYS			
Janumet xr	Sitagliptin-Metformin HCl Tab ER 24HR 50-1000 MG	50-1000 MG	60	Tablets	30	DAYS			
Janumet xr	Sitagliptin-Metformin HCl Tab ER 24HR 50-500 MG	50-500 MG	30	Tablets	30	DAYS			

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Januvia	Sitagliptin Phosphate Tab 100 MG (Base Equiv)	100 MG	30	Tablets	30	DAYS			
Januvia	Sitagliptin Phosphate Tab 25 MG (Base Equiv)	25 MG	30	Tablets	30	DAYS			
Januvia	Sitagliptin Phosphate Tab 50 MG (Base Equiv)	50 MG	30	Tablets	30	DAYS			
Jentadueto	Linagliptin-Metformin HCl Tab 2.5-1000 MG	2.5-1000 MG	60	Tablets	30	DAYS			
Jentadueto	Linagliptin-Metformin HCl Tab 2.5-500 MG	2.5-500 MG	60	Tablets	30	DAYS			
Jentadueto	Linagliptin-Metformin HCl Tab 2.5-850 MG	2.5-850 MG	60	Tablets	30	DAYS			
Jentadueto xr	Linagliptin-Metformin HCl Tab ER 24HR 2.5-1000 MG	2.5-1000 MG	60	Tablets	30	DAYS			
Jentadueto xr	Linagliptin-Metformin HCl Tab ER 24HR 5-1000 MG	5-1000 MG	30	Tablets	30	DAYS			
Kazano	Alogliptin-Metformin HCl Tab 12.5-1000 MG	12.5-1000 MG	60	Tablets	30	DAYS			
Kazano	Alogliptin-Metformin HCl Tab 12.5-500 MG	12.5-500 MG	60	Tablets	30	DAYS			
Kombiglyze xr	Saxagliptin-Metformin HCl Tab ER 24HR 2.5-1000 MG	2.5-1000 MG	60	Tablets	30	DAYS			
Kombiglyze xr	Saxagliptin-Metformin HCl Tab ER 24HR 5-1000 MG	5-1000 MG	30	Tablets	30	DAYS			
Kombiglyze xr	Saxagliptin-Metformin HCl Tab ER 24HR 5-500 MG	5-500 MG	30	Tablets	30	DAYS			
Nesina	Alogliptin Benzoate Tab 12.5 MG (Base Equiv)	12.5 MG	30	Tablets	30	DAYS			
Nesina	Alogliptin Benzoate Tab 25 MG (Base Equiv)	25 MG	30	Tablets	30	DAYS			
Nesina	Alogliptin Benzoate Tab 6.25 MG (Base Equiv)	6.25 MG	30	Tablets	30	DAYS			
Onglyza	Saxagliptin HCl Tab 2.5 MG (Base Equiv)	2.5 MG	30	Tablets	30	DAYS			
Onglyza	Saxagliptin HCl Tab 5 MG (Base Equiv)	5 MG	30	Tablets	30	DAYS			
Oseni	Alogliptin-Pioglitazone Tab 12.5-15 MG	12.5-15 MG	30	Tablets	30	DAYS			
Oseni	Alogliptin-Pioglitazone Tab 12.5-30 MG	12.5-30 MG	30	Tablets	30	DAYS			
Oseni	Alogliptin-Pioglitazone Tab 12.5-45 MG	12.5-45 MG	30	Tablets	30	DAYS			
Oseni	Alogliptin-Pioglitazone Tab 25-15 MG	25-15 MG	30	Tablets	30	DAYS			

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Oseni	Alogliptin-Pioglitazone Tab 25-30 MG	25-30 MG	30	Tablets	30	DAYS			
Oseni	Alogliptin-Pioglitazone Tab 25-45 MG	25-45 MG	30	Tablets	30	DAYS			
Tradjenta	Linagliptin Tab 5 MG	5 MG	30	Tablets	30	DAYS			
Zituvio	sitagliptin tab	25 MG	30	Tablets	30	DAYS			
Zituvio	sitagliptin tab	50 MG	30	Tablets	30	DAYS			
Zituvio	sitagliptin tab	100 MG	30	Tablets	30	DAYS			

CLIENT SUMMARY – STEP THERAPY

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Janumet	sitagliptin-metformin hcl tab	50-1000 MG ; 50-500 MG	Medicaid
Janumet xr	sitagliptin-metformin hcl tab er	100-1000 MG ; 50-1000 MG ; 50-500 MG	Medicaid
Januvia	sitagliptin phosphate tab	100 MG ; 25 MG ; 50 MG	Medicaid
Jentadueto	linagliptin-metformin hcl tab	2.5-1000 MG ; 2.5-500 MG ; 2.5-850 MG	Medicaid
Jentadueto xr	linagliptin-metformin hcl tab er	2.5-1000 MG ; 5-1000 MG	Medicaid
Kombiglyze xr	saxagliptin-metformin hcl tab er	2.5-1000 MG ; 5-1000 MG ; 5-500 MG	Medicaid
Nesina	alogliptin benzoate tab	12.5 MG ; 25 MG ; 6.25 MG	Medicaid
Onglyza	saxagliptin hcl tab	2.5 MG ; 5 MG	Medicaid
Tradjenta	linagliptin tab	5 MG	Medicaid

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Janumet	Sitagliptin-Metformin HCl Tab 50-1000 MG	50-1000 MG	Medicaid
Janumet	Sitagliptin-Metformin HCl Tab 50-500 MG	50-500 MG	Medicaid
Janumet xr	Sitagliptin-Metformin HCl Tab ER 24HR 100-1000 MG	100-1000 MG	Medicaid
Janumet xr	Sitagliptin-Metformin HCl Tab ER 24HR 50-1000 MG	50-1000 MG	Medicaid
Janumet xr	Sitagliptin-Metformin HCl Tab ER 24HR 50-500 MG	50-500 MG	Medicaid
Januvia	Sitagliptin Phosphate Tab 100 MG (Base Equiv)	100 MG	Medicaid
Januvia	Sitagliptin Phosphate Tab 25 MG (Base Equiv)	25 MG	Medicaid
Januvia	Sitagliptin Phosphate Tab 50 MG (Base Equiv)	50 MG	Medicaid
Jentadueto	Linagliptin-Metformin HCl Tab 2.5-1000 MG	2.5-1000 MG	Medicaid
Jentadueto	Linagliptin-Metformin HCl Tab 2.5-500 MG	2.5-500 MG	Medicaid
Jentadueto	Linagliptin-Metformin HCl Tab 2.5-850 MG	2.5-850 MG	Medicaid

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Jentadueto xr	Linagliptin-Metformin HCl Tab ER 24HR 2.5-1000 MG	2.5-1000 MG	Medicaid
Jentadueto xr	Linagliptin-Metformin HCl Tab ER 24HR 5-1000 MG	5-1000 MG	Medicaid
Kazano	Alogliptin-Metformin HCl Tab 12.5-1000 MG	12.5-1000 MG	Medicaid
Kazano	Alogliptin-Metformin HCl Tab 12.5-500 MG	12.5-500 MG	Medicaid
Kombiglyze xr	Saxagliptin-Metformin HCl Tab ER 24HR 2.5-1000 MG	2.5-1000 MG	Medicaid
Kombiglyze xr	Saxagliptin-Metformin HCl Tab ER 24HR 5-1000 MG	5-1000 MG	Medicaid
Kombiglyze xr	Saxagliptin-Metformin HCl Tab ER 24HR 5-500 MG	5-500 MG	Medicaid
Nesina	Alogliptin Benzoate Tab 12.5 MG (Base Equiv)	12.5 MG	Medicaid
Nesina	Alogliptin Benzoate Tab 25 MG (Base Equiv)	25 MG	Medicaid
Nesina	Alogliptin Benzoate Tab 6.25 MG (Base Equiv)	6.25 MG	Medicaid
Onglyza	Saxagliptin HCl Tab 2.5 MG (Base Equiv)	2.5 MG	Medicaid
Onglyza	Saxagliptin HCl Tab 5 MG (Base Equiv)	5 MG	Medicaid
Oseni	Alogliptin-Pioglitazone Tab 12.5-15 MG	12.5-15 MG	Medicaid
Oseni	Alogliptin-Pioglitazone Tab 12.5-30 MG	12.5-30 MG	Medicaid
Oseni	Alogliptin-Pioglitazone Tab 12.5-45 MG	12.5-45 MG	Medicaid
Oseni	Alogliptin-Pioglitazone Tab 25-15 MG	25-15 MG	Medicaid
Oseni	Alogliptin-Pioglitazone Tab 25-30 MG	25-30 MG	Medicaid
Oseni	Alogliptin-Pioglitazone Tab 25-45 MG	25-45 MG	Medicaid
Tradjenta	Linagliptin Tab 5 MG	5 MG	Medicaid
Zituvio	sitagliptin tab	25 MG	Medicaid
Zituvio	sitagliptin tab	50 MG	Medicaid
Zituvio	sitagliptin tab	100 MG	Medicaid

STEP THERAPY CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	TARGET AGENT(S) **Januvia** (sitagliptin) **Janumet** (sitagliptin/metformin) **Janumet XR** (sitagliptin/metformin ER) **Jentadueto** (linagliptin/metformin) **Jentadueto XR** (linagliptin/metformin ER) **Kombiglyze XR** (saxagliptin/metformin ER) **Nesina** (alogliptin) **Onglyza** (saxagliptin) **Tradjenta** (linagliptin) **Target Agent(s)** will be approved when ONE of the following is met: 1. Information has been provided that indicates the patient has been being treated with the requested agent within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent within the past 90 days AND is at risk if therapy is changed **OR** 3. 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**

Module	Clinical Criteria for Approval
	C. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** 4. The patient's medication history includes use of an agent containing metformin or insulin **OR** 5. The prescriber has stated that the patient has tried insulin or an agent containing metformin AND ONE of the following: A. Insulin or an agent containing metformin 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** 6. The patient has an intolerance or hypersensitivity to ONE of the following: metformin or insulin **OR** 7. The patient has an FDA labeled contraindication to ALL of the following: metformin and insulins **OR** 8. The prescriber has provided documentation that metformin AND insulins 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 **Length of Approval:** 12 months NOTE: If Quantity Limit program also applies, please refer to Quantity Limit criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL Standalone	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months