Dipeptidyl Peptidase-4 (DPP-4) Inhibitors, DPP-4 Inhibitor Combination Drugs, Cycloset® (bromocriptine)

Policy # 00306
Original Effective Date: 05/22/2013
Current Effective Date: 10/18/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

For Patients With "Step Therapy" (generic before brand) ONLY:
Based on review of available data, the Company may consider dipeptidyl peptidase-4 (DPP-4) inhibitors including, but not limited to Januvia®‡ (sitagliptin), Onglyza®‡ (saxagliptin), Tradjenta®‡ (linagliptin), branded Alogliptin, and Nesina®‡ (alogliptin) OR dipeptidyl peptidase-4 inhibitor combination drugs including, but not limited to Janumet®‡ (sitagliptin/metformin), Janumet®‡ XR (sitagliptin/metformin extended release), Juvisync®‡ (sitagliptin/simvastatin), Kombiglyze XR®‡ (saxagliptin/metformin extended release), Jentadueto®‡ (linagliptin/metformin), Jentadueto®‡ XR (linagliptin/metformin extended release), branded Alogliptin/Metformin, Kazano®‡ (alogliptin/metformin), branded Alogliptin/Pioglitazone, and Oseni®‡ (alogliptin/pioglitazone) OR Cycloset®‡ (bromocriptine) to be **eligible for coverage** when the below patient selection criteria are met:

Patient Selection Criteria
Coverage eligibility will be considered for the following drugs when their respective patient selection criteria are met:

- For dipeptidyl peptidase-4 (DPP-4) inhibitors (combo/non-combo) or Cycloset (bromocriptine): Patient has tried a metformin or metformin-containing combination product (brand or generic); OR
- For dipeptidyl peptidase-4 (DPP-4) inhibitors (combo/non-combo) or Cycloset (bromocriptine): There is clinical evidence or patient history that suggests metformin products will be/were ineffective or will/did cause an adverse reaction to the patient; OR
- For dipeptidyl peptidase-4 (DPP-4) inhibitors (non-combo) or Cycloset (bromocriptine): Patient is initiating dual therapy with metformin OR patient has ONE of the following conditions:
    - Hepatic impairment; OR
    - Alcohol dependence; OR
    - Renal insufficiency or renal disease; OR
    - Cardiomyopathy, heart failure, unstable, angina, or a myocardial infarction; OR
    - A condition that could potentially increase the risk of hypoperfusion, hypoxemia, or dehydration; OR
    - Chronic metabolic acidosis

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When Services Are Considered Not Medically Necessary
Based on review of available data, the Company considers the use of dipeptidyl peptidase-4 (DPP-4) inhibitors (combo/non-combo) or Cycloset (bromocriptine) when patient selection criteria are not met or for usage not included in the above patient selection criteria to be **not medically necessary**.**

For Patients With "Prior Authorization" ONLY:
Based on review of available data, the Company may consider Onglyza (saxagliptin), Kombiglyze XR (saxagliptin/metformin extended release), branded Alogliptin, Nesina (alogliptin), branded Alogliptin/Metformin, or Kazano (alogliptin/metformin) to be **eligible for coverage** when the below patient selection criterion is met:

Patient Selection Criteria
Coverage eligibility will be considered for Onglyza (saxagliptin), Kombiglyze XR (saxagliptin/metformin extended release), branded Alogliptin, Nesina (alogliptin), branded Alogliptin/Metformin, or Kazano (alogliptin/metformin) when the following criterion is met:

- There is clinical evidence or patient history that suggests the use of Januvia (sitagliptin), Janumet (sitagliptin/metformin), Janumet XR (sitagliptin/metformin extended release), Tradjenta (linagliptin), Jentadueto (linagliptin/metformin), or Jentadueto XR (linagliptin/metformin extended release) will be/was ineffective or will/did cause an adverse reaction to the patient.

When Services Are Considered Not Medically Necessary
Based on review of available data, the Company considers the use of Onglyza (saxagliptin), Kombiglyze XR (saxagliptin/metformin extended release), branded Alogliptin, Nesina (alogliptin), branded Alogliptin/Metformin, or Kazano (alogliptin/metformin) WITHOUT clinical evidence or patient history that suggests the use of Januvia (sitagliptin), Janumet (sitagliptin/metformin), Janumet XR (sitagliptin/metformin extended release), Tradjenta (linagliptin), Jentadueto (linagliptin/metformin), or Jentadueto XR (linagliptin/metformin extended release) will be/was ineffective or will/did cause an adverse reaction to the patient to be **not medically necessary**.**

For Patients With BOTH "Prior Authorization" AND "Step Therapy":
Based on review of available data, the Company may consider dipeptidyl peptidase-4 (DPP-4) inhibitors including, but not limited to Januvia (sitagliptin), Onglyza (saxagliptin), Tradjenta (linagliptin), branded Alogliptin, and Nesina (alogliptin) OR dipeptidyl peptidase-4 inhibitor combination drugs including, but not limited to Janumet (sitagliptin/metformin), Janumet XR (sitagliptin/metformin extended release), Juvisync (sitagliptin/simvastatin), Kombiglyze®‡ (saxagliptin/metformin), Jentadueto (linagliptin/metformin), Jentadueto XR (linagliptin/metformin extended release), branded Alogliptin/Metformin, Kazano (alogliptin/metformin), branded Alogliptin/Pioglitazone, and Oseni (alogliptin/pioglitazone) OR Cycloset (bromocriptine) to be **eligible for coverage** when the below patient selection criteria are met:

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Patient Selection Criteria

Coverage eligibility will be considered for the following drugs when their respective patient selection criteria are met:

- For Cycloset (bromocriptine) OR dipeptidyl peptidase-4 (DPP-4) inhibitors (combo/non-combo, EXCEPT Onglyza (saxagliptin), Kombiglyze XR (saxagliptin/metformin extended release), branded Alogliptin, Nesina (alogliptin), branded Alogliptin/Metformin, and Kazano (alogliptin/metformin)):
    - Patient has tried a metformin or metformin-containing combination product (brand or generic); OR
    - There is clinical evidence or patient history that suggests metformin products will be/were ineffective or will/did cause an adverse reaction to the patient
- For Cycloset (bromocriptine) OR dipeptidyl peptidase-4 (DPP-4) inhibitors (non-combo, EXCEPT Onglyza (saxagliptin), branded Alogliptin, and Nesina (alogliptin)): Patient is initiating dual therapy with metformin OR patient has ONE of the following conditions:
    - Hepatic impairment; OR
    - Alcohol dependence; OR
    - Renal insufficiency or renal disease; OR
    - Cardiomyopathy, heart failure, unstable, angina, or a myocardial infarction; OR
    - A condition that could potentially increase the risk of hypoperfusion, hypoxemia, or dehydration; OR
    - Chronic metabolic acidosis
- For Onglyza (saxagliptin), Kombiglyze XR (saxagliptin/metformin extended release), branded Alogliptin, Nesina (alogliptin), branded Alogliptin/Metformin, and Kazano (alogliptin/metformin):
    - The patient must meet ONE of the following:
        - Patient has tried a metformin or metformin-containing combination product (brand or generic) UNLESS there is clinical evidence or patient history that suggests metformin products will be/were ineffective or will/did cause an adverse reaction to the patient; OR
        - For Onglyza (saxagliptin), branded Alogliptin, and Nesina (alogliptin) ONLY: Patient is initiating dual therapy with metformin OR patient has ONE of the following conditions:
            - Hepatic impairment; OR
            - Alcohol dependence; OR
            - Renal insufficiency or renal disease; OR
            - Cardiomyopathy, heart failure, unstable, angina, or a myocardial infarction; OR
            - A condition that could potentially increase the risk of hypoperfusion, hypoxemia, or dehydration; OR
            - Chronic metabolic acidosis
    - AND The patient must ALSO meet this criterion:
        - There is clinical evidence or patient history that suggests the use of Januvia (sitagliptin), Janumet (sitagliptin/metformin), Janumet XR (sitagliptin/metformin

extended release), Tradjenta (linagliptin), Jentadueto (linagliptin/metformin), or Jentadueto XR (linagliptin/metformin extended release) will be/was ineffective or will/did cause an adverse reaction to the patient.

When Services Are Considered Not Medically Necessary
Based on review of available data, the Company considers the use of the requested dipeptidyl peptidase-4 (DPP-4) inhibitors (combo/non-combo) or Cycloset (bromocriptine) when patient selection criteria are not met or for usage not included in the above patient selection criteria to be **not medically necessary**.**

Schematic
The schematic below gives a general overview of coverage when the appropriate criteria are met. In general, step 1 products should be used first, followed by preferred products, and then non-preferred products. Note that Juvisync (sitagliptin/simvastatin), branded Alogliptin/Pioglitazone, Oseni (alogliptin/pioglitazone), and Cycloset (bromocriptine) are ONLY subject to step therapy.

Program	Step 1	Preferred	Non-Preferred
Step Therapy ONLY	metformin/metformin containing products	Any Brand DPP-4	
Prior Authorization ONLY	N/A	Januvia, Janumet, Janumet XR, Tradjenta, Jentadueto, Jentadueto XR	Onglyza, Kombiglyze XR, branded Alogliptin, Nesina, branded Alogliptin/Metformin, Kazano
Prior Authorization AND Step Therapy	metformin/metformin containing products	Januvia, Janumet, Janumet XR, Tradjenta, Jentadueto, Jentadueto XR	Onglyza, Kombiglyze XR, branded Alogliptin, Nesina, branded Alogliptin/Metformin, Kazano

Background/Overview
Dipeptidyl peptidase-4 inhibitors and DPP-4 inhibitor combination drugs are approved for patients with Type 2 Diabetes Mellitus. Cycloset (bromocriptine) is also approved for patients with Type 2 Diabetes Mellitus as an adjunct to diet and exercise.

Rationale/Source
The patient selection criteria presented in this policy takes into consideration clinical evidence or patient history that suggests metformin products will be ineffective or cause an adverse reaction to the patient. This

policy also takes into consideration other situations in which using metformin as a first-line treatment is not appropriate. Based on a review of the data, in the absence of the above mentioned caveats, there is no advantage of using a DPP-4 inhibitor, DPP-4 inhibitor combination drug, or Cycloset (bromocriptine) over the available brand or generic metformin products. For patients with prior authorization, based on a review of the available data and in the absence of any of the caveats mentioned, there is no advantage of using Onglyza (saxagliptin), Kombiglyze XR (saxagliptin/metformin extended release), branded Alogliptin, Nesina (alogliptin), branded Alogliptin/Metformin, or Kazano (alogliptin/metformin) over Januvia (sitagliptin), Janumet (sitagliptin/metformin), Janumet XR (sitagliptin/metformin extended release), Tradjenta (linagliptin), Jentadueto (linagliptin/metformin), or Jentadueto XR (linagliptin/metformin extended release).

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3. Onglyza tablets [package insert]. Princeton, NJ. Bristol-Meyers Squibb Company; December 2011.
4. Nesina tablets [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; January 2013.
5. Janumet tablets [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.;. February 2013.
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9. Kazano tablets [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; January 2013.
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Policy History

Original Effective Date: 05/22/2013
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05/02/2013	Medical Policy Committee review
05/22/2013	Medical Policy Implementation Committee approval. New policy.
05/01/2014	Medical Policy Committee review
05/21/2014	Medical Policy Implementation Committee approval. No change to coverage.
10/02/2014	Medical Policy Committee review
10/15/2014	Medical Policy Implementation Committee approval. Implemented a PA for non-preferred products to use preferred products, which are Januvia, Janumet, Janumet XR, Onglyza, and Kombiglyze XR.
10/08/2015	Medical Policy Committee review.
10/21/2015	Medical Policy Implementation Committee approval. Considering other preferred products within next few months based on more updated modeling discussions. Will update policy in February 2016 with decisions. Will halt posting until that point.
02/04/2016	Medical Policy Committee review
02/17/2016	Medical Policy Implementation Committee approval. No change to coverage. Will not change preferred products.
06/30/2016	Medical Policy Committee review
07/20/2016	Medical Policy Implementation Committee approval. Added branded Alogliptin, branded Alogliptin/Metformin, Alogliptin/Pioglitazone and Jentadueto XR to the policy.
10/06/2016	Medical Policy Committee review
10/19/2016	Medical Policy Implementation Committee approval. Moving Onglyza and Kombiglyze ER to non-preferred. Moving Tradjenta and Jentadueto/XR to preferred.
10/05/2017	Medical Policy Committee review
10/18/2017	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 10/2018

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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