GLP-1 Agonists for Diabetes

Policy # 00324
Original Effective Date: 11/16/2011
Current Effective Date: 01/01/2019

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.*

Based on review of the available data, the Company may consider glucagon like peptide 1 (GLP-1) agonists that are FDA approved for the treatment of diabetes, including but not limited to Byetta®‡ † (exenatide), Bydureon®‡/Bydureon BCise (exenatide ER), Victoza®‡ † (liraglutide), Tanzeum™‡ (albiglutide), Trulicity™‡ (dulaglutide), Adlyxin®‡ (lixisenatide), and Ozempic®‡ (semaglutide), to be **eligible for coverage** when the patient selection criteria below are met for the requested drug:

Patient Selection Criteria
Coverage eligibility will be considered when the patient selection criteria are met for the requested drug:

- For Victoza (liraglutide), Trulicity (dulaglutide), or Ozempic (semaglutide) requests:
  - Patient has type 2 diabetes mellitus; OR
- For Byetta (exenatide), Bydureon/Bydureon BCise (exenatide ER), Tanzeum (albiglutide), or Adlyxin (lixisenatide) requests:
  - Patient has type 2 diabetes mellitus; AND
  - Patient has tried and failed (e.g. intolerance or inadequate response) at least TWO of the following products: Victoza (liraglutide), Trulicity (dulaglutide), or Ozempic (semaglutide).
    *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*

When Services Are Considered Not Medically Necessary
Based on review of available data, the Company considers the use of Byetta (exenatide), Bydureon/Bydureon BCise (exenatide ER), Tanzeum (albiglutide), or Adlyxin (lixisenatide) WITHOUT having tried and failed at least TWO of the following products: Victoza (liraglutide), Trulicity (dulaglutide), or Ozempic (semaglutide) to be **not medically necessary.****

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of GLP-1 agonists that are FDA approved for the treatment of diabetes for any non-FDA approved indication for that specific drug to be **investigational.***

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Schematic

Preferred	Non-Preferred
Trulicity Victoza Ozempic	Byetta† Bydureon/Bydureon BCise Tanzeum Adlyxin

Background/Overview

Byetta, Bydureon/Bydureon BCise, Victoza, Tanzeum, Trulicity, Adlyxin, and Ozempic are antihyperglycemic agents for subcutaneous injection. These products are incretin mimetic agents that bind and activate the human GLP-1 receptor. Activation of this receptor increases glucose-dependent insulin secretion by pancreatic beta-cells and suppresses glucagon secretion and slows gastric emptying. Byetta, Bydureon/Bydureon BCise, Victoza, Tanzeum, Trulicity, Adlyxin, and Ozempic are FDA approved in adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. Byetta is administered twice daily. Bydureon/Bydureon BCise, Tanzeum, Trulicity, and Ozempic are administered once weekly, and Victoza and Adlyxin are administered once daily.

The active ingredients in the non-preferred products have not demonstrated superiority in head to head studies comparing preferred and non-preferred products.

This policy is also intended to ensure that the GLP-1 agonist products approved for the treatment of type 2 diabetes are used for the indication of type 2 diabetes only.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
All of the products mentioned in this policy are FDA approved for the treatment of type 2 diabetes mellitus.

Rationale/Source

As monotherapy, Byetta 5- or 10-mcg twice daily in adjunct to diet and exercise reduced glycosylated hemoglobin (HbA1c) 0.5 to 0.7% (placebo corrected); a placebo corrected weight loss of 2.7 kg to 2.9 kg was noted at the end of the 24-week trial. In general, Byetta appears to lower HbA1c by 0.5% to 1%. In addition to HbA1c reduction, Byetta reduces food intake, and on average produces a 2 kg to 3 kg weight loss over a 6-month period in diabetic patients. Byetta 10mcg twice daily as an adjunct to metformin, a sulfonylurea, or both in patients with type 2 diabetes decreased body weight by 1.6 kg to 2.8 kg after 30 weeks. In an interim analysis involving a 52-week open-label uncontrolled extension study, which followed the 30 week double-blind period, the average weight loss in type 2 diabetics (n = 314) after a total of 82 weeks of Byetta therapy was 4.4 kg. A similar analysis of an interim report noted weight loss in type 2 diabetics (n = 92) after 82 weeks of Byetta treatment was 5.3kg. In a multicenter, open-label, randomized, controlled trial in patients with type 2 diabetes (n = 551), at 26 weeks, treatment with Byetta led to a 2.3 kg reduction in body weight compared with a 1.8 kg increase for patients treated with insulin glargine (Lantus®)‡†. Addition of Byetta to a thiazolidinedione ([TZD] with or without metformin) resulted in a 1.51 kg

mean reduction in bodyweight after 16 weeks. Reductions in bodyweight in type 2 diabetic patients treated with Byetta have been sustained for up to two years.

As monotherapy in a 52-week trial, Victoza 1.2 mg and 1.8 mg in adjunct to diet and exercise resulted in mean HbA1c reduction of 0.8% to 1.1% and a 2.1 kg to 2.5 kg weight reduction. Victoza was studied in combination with one or two other oral anti-diabetic agents in four 26-week studies. When added to metformin, Victoza 1.8 mg and 1.2 mg resulted in a mean placebo corrected HbA1c and weight reduction of 1.1% and 1.1 kg to 1.3 kg, respectively. As add-on to sulfonylurea (glimeperide), Victoza 1.2 mg and 1.8 mg treatment resulted in a placebo corrected mean HbA1c reduction of 1.3% to 1.4%. As part of a triple therapy combination with metformin and glimeperide, Victoza 1.8 mg reduced HbA1c (placebo corrected mean) by 1.1% and resulted in a mean weight reduction of 1.4 kg (placebo corrected). When added to metformin and rosiglitazone mean placebo corrected reduction in HbA1c and weight with Victoza (1.8 mg and 1.2 mg) were 0.9% (both doses) and 2.6 kg and 1.6 kg, respectively. In a head-to-head trial with Byetta, weight was significantly reduced in both Byetta (10 mcg twice daily) and Victoza (1.8 mg daily) and was non-significant between groups (-2.87 kg vs. -3.24 kg, respectively).

A randomized, open-label 24-week comparative trial was conducted with Bydureon and Byetta for safety and efficacy in 252 patients with type 2 diabetes. These patients had inadequate gylcemic control with diet and exercise alone or with oral antidiabetic therapy, including metformin, a sulfonylurea, a TZD, or combination of two of those therapies. Patients were treated with diet and exercise alone (19%), a single oral antidiabetic agent (47%), or combination therapy of oral antidiabetic agents (35%). The mean baseline HbA1c was 8.4%. Patients were randomly assigned to receive Bydureon 2 mg once every seven days (weekly) or Byetta (10 mcg twice-daily), in addition to existing oral antidiabetic agents. Patients assigned to Byetta initiated treatment with 5 mcg twice-daily then increased the dose to 10 mcg twice-daily after 4 weeks. The primary endpoint was change in HbA1c from baseline to Week 24 (or the last value at time of early discontinuation). Change in body weight was a secondary endpoint. Treatment with Bydureon was superior to Byetta for mean HbA1c reduction over 24 weeks.

Tanzeum was studied against placebo in a 52 week trial at doses of 30 mg weekly and 50 mg weekly. The mean change in HbA1c ranged from -0.7% to -0.9% and fasting plasma glucose (FPG) decreased between 16 and 25 mg/dL. Subjects also saw weight loss ranging from 0.4 to 0.9 kg. In a separate 104 week trial, Tanzeum added to metformin decreased the HbA1c by 0.63% and patients experienced a weight loss of 1.2 kg. Tanzeum has also been studied with a TZD ± metformin and reduced HbA1c by 0.8%.

Trulicity was studied in various trials as monotherapy as well as in addition to oral therapies and in addition to insulin. As monotherapy, Trulicity lowered the HbA1c from 0.7-0.8% vs. metformin's lowering of 0.6%. Trulicity as monotherapy also lowered the fasting plasma glucose by 26 to 29 mg/dL vs. a lowering of 24 mg/dL with metformin. In the combo therapy trials, the HbA1c lowering ranged from 0.8 to 1.6% depending on the treatment that Trulicity was combined with.

Adlyxin was studied in various trials as monotherapy as well as in addition to oral therapies and in addition to insulin. As monotherapy, Adlyxin lowered the HbA1c by 0.83% from baseline (0.65% difference from

placebo). Adlyxin also lowered fasting plasma glucose by 15.84 mg/dL in the monotherapy trial. The range of lowering of HbA1c in the combination studies ranges from 0.7-0.91% depending on what drug Adlyxin was combined with.

Ozempic has been studied as monotherapy and in combination with metformin, metformin and sulfonylureas, metformin and/or thiazolidinedione, and basal insulin in patients with type 2 diabetes mellitus. The efficacy of Ozempic was compared with placebo, sitagliptin, Bydureon, and insulin glargine. Most trials evaluated the use of Ozempic 0.5 mg, and 1 mg, with the exception of the trial comparing Ozempic and Bydureon where only the 1 mg dose was studied. In patients with type 2 diabetes mellitus, Ozempic produced clinically relevant reduction from baseline in HbA1c compared with placebo. The various HbA1c lowering ranged from 1.1-1.6% depending on the clinical comparison.

Based on a review of the available data and in the absence of any of the caveats mentioned, there is no advantage of using the non-preferred agents mentioned in this policy over the preferred agents mentioned in this policy.

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Policy History

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11/03/2011	Medical Policy Committee review
11/16/2011	Medical Policy Implementation Committee approval. New policy.
11/01/2012	Medical Policy Committee review
11/28/2012	Medical Policy Implementation Committee approval. Added Bydureon (exenatide ER) to the title and coverage statement.
11/07/2013	Medical Policy Committee review
11/20/2013	Medical Policy Implementation Committee approval. Revision to coverage language without changing the intent of the policy. Coverage eligibility unchanged.
11/06/2014	Medical Policy Committee review
11/21/2014	Medical Policy Implementation Committee approval. Changed title. Added Tanzeum to the policy. Updated background information and rationale to reflect new product and title change.
04/02/2015	Medical Policy Committee review
04/20/2015	Medical Policy Implementation Committee approval. Changed title. Added Trulicity to policy. Updated background and rationale.
04/07/2016	Medical Policy Committee review
04/20/2016	Medical Policy Implementation Committee approval. No change to coverage.
10/06/2016	Medical Policy Committee review
10/19/2016	Medical Policy Implementation Committee approval. Chose preferred products in this class (Byetta, Bydureon, Victoza, and Trulicity).

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03/02/2017	Medical Policy Committee review
03/15/2017	Medical Policy Implementation Committee approval. Clarified to use two preferred products.
03/01/2018	Medical Policy Committee review
03/21/2018	Medical Policy Implementation Committee approval. No change to coverage.
07/05/2018	Medical Policy Committee review
07/11/2018	Medical Policy Implementation Committee approval. Added Ozempic and Bydureon BCise to the policy.
09/06/2018	Medical Policy Committee review
09/19/2018	Medical Policy Implementation Committee approval. Moved Byetta and Bydureon/Bydureon Bcise to non-preferred

Next Scheduled Review Date: 09/2019

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.