GLP-1 Agonists for Diabetes

Policy # 00324
Original Effective Date: 11/16/2011
Current Effective Date: 01/01/2017

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.

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® (exenatide ER), Victoza® (liraglutide), Tanzeum™ (albiglutide), Trulicity™ (dulaglutide), and Adlyxin® (lixisenatide) to be eligible for coverage when the patient selection criteria below are met for the requested drug:

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

- For Byetta® (exenatide), Bydureon® (exenatide ER), Victoza® (liraglutide), or Trulicity® (dulaglutide) requests:
  - Patient has type 2 diabetes mellitus

- For Tanzeum™ (albiglutide) or Adlyxin® (lixisenatide) requests:
  - Patient has type 2 diabetes mellitus; AND
  - There is clinical evidence or patient history that suggests the use of Byetta® (exenatide), Bydureon® (exenatide ER), Victoza® (liraglutide), or Trulicity® (dulaglutide) will be/was ineffective or will/did cause an adverse reaction to the patient. (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 Tanzeum™ (albiglutide) or Adlyxin® (lixisenatide) WITHOUT clinical evidence or patient history that suggests the use of Byetta® (exenatide), Bydureon® (exenatide ER), Victoza® (liraglutide), or Trulicity® (dulaglutide) will be/was ineffective or will/did cause an adverse reaction to the patient 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 glucagon like peptide 1 (GLP-1) agonists that are FDA approved for the treatment of diabetes for any other non-FDA approved indication for that specific drug to be investigational.*
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### Schematic

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Non-Preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byetta†</td>
<td>Tanzeum</td>
</tr>
<tr>
<td>Bydureon†</td>
<td>Adlyxin</td>
</tr>
<tr>
<td>Trulicity</td>
<td></td>
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<tr>
<td>Victoza</td>
<td></td>
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</tbody>
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### Background/Overview

Byetta, Bydureon, Victoza, Tanzeum, Trulicity, and Adlyxin are antihyperglycemic agents for subcutaneous (SC) injection. These products are incretin mimetic agents that bind and activate the human glucagon-like peptide-1 (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, Victoza, Tanzeum, Trulicity, and Adlyxin are Food and Drug Administration (FDA)-approved in adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. Byetta is administered twice daily (BID), Bydureon, Tanzeum, and Trulicity are administered once weekly (QW [every seven days]), and Victoza and Adlyxin are administered once daily (QD).

The active ingredients in these products have not been studied head to head and therefore no superiority claims can be made.

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 Approval

In 2009 Amylin Pharmaceuticals Inc. and Eli Lilly and Company announced that the U.S. FDA has approved an expanded indication for Byetta (exenatide) injection.

In 2010 the U.S. FDA approved Victoza (liraglutide), a once-daily injection to treat type 2 diabetes in some adults.

In 2012 the U.S. FDA approved Bydureon (exenatide ER), an extended-release weekly injection to treat type 2 diabetes in adults.

In 2014 the U.S. FDA approved Tanzeum (albiglutide), an extended-release weekly injection to treat type 2 diabetes in adults.

In 2014 the U.S. FDA approved Trulicity (dulaglutide), an extended-release weekly injection to treat type 2 diabetes in adults.

In 2016, the U.S.FDA approved Adlyxin (lixisenatide), a once-daily injection to treat type 2 diabetes in adults.
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Rationale/Source
This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

As monotherapy, Byetta 5- or 10-mcg BID in adjunct to diet and exercise reduced glycosylated hemoglobin (HbA1c) 0.5 to 0.7% (placebo corrected); a placebo corrected weight loss of 2.7kg to 2.9kg was noted at the end of the 24-week trial. In general, exenatide appears to lower HbA1c by 0.5% to 1%. In addition to HbA1c reduction, Byetta reduces food intake, and on average produces a 2kg to 3kg weight loss over a 6-month period in diabetic patients. Byetta 10mcg BID as an adjunct to metformin, a sulfonylurea, or both in patients with type 2 diabetes decreased body weight by 1.6kg to 2.8kg 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 4.4kg. 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 2.3kg 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 1.51kg 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 1.2mg and 1.8mg in adjunct to diet and exercise resulted in mean HbA1c reduction of 0.8% to 1.1% and a 2.1kg to 2.5kg 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 1.8mg and 1.2mg resulted in a mean placebo corrected HbA1c and weight reduction of 1.1% and 1.1kg to 1.3kg, respectively. As add-on to sulfonylurea (glimeperide), Victoza 1.2mg and 1.8mg 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 1.8mg reduced HbA1c (placebo corrected mean) by 1.1% and resulted in a mean weight reduction of 1.4kg (placebo corrected). When added to metformin and rosiglitazone mean placebo corrected reduction in HbA1c and weight with Victoza (1.8mg and 1.2mg) were 0.9% (both doses) and 2.6kg and 1.6kg, respectively. In a head-to-head trial with exenatide, weight was significantly reduced in both Byetta (10µg BID) and Victoza (1.8mg QD) and was non-significant between groups (-2.87kg vs. -3.24kg, 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 glycemic 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 2mg once every seven days (weekly) or Byetta (10mcg twice-daily), in addition to existing oral antidiabetic agents. Patients assigned to
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Byetta initiated treatment with 5mcg twice-daily then increased the dose to 10mcg 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 30mg weekly and 50mg 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 0.9kg. In a separate 104 week trial, Tanzeum added to metformin decreased the HbA1c by 0.63% and patients experienced a weight loss of 1.2kg. 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 29mg/dL vs. a lowering of 24mg/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.

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

References
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04/20/2015  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).

Next Scheduled Review Date:  10/2017

*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. 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.

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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.