Pharmacy Policy Bulletin

Title: Glucagon-like Peptide-1 (GLP-1) Receptor Agonist

Policy #: Rx.01.275

Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.

Members are advised to use participating pharmacies in order to receive the highest level of benefits.

Intent:

The intent of this policy is to communicate the medical necessity criteria for **exenatide (Byetta®), exenatide extended release (Bydureon®/Bydureon BCise®), tirzepatide (Mounjaro™), semaglutide (Ozempic®, Rybelsus®), dulaglutide (Trulicity®), liraglutide (Victoza®), and lixisenatide (Adlyxin®)** as provided under the member's prescription drug benefit.

Description:

Exenatide is a GLP-1 receptor agonist that enhances glucose-dependent insulin secretion by the pancreatic beta-cell, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying.

Byetta® (exenatide) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Bydureon®/Bydureon BCise® (exenatide extended release) is indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus.

Tirzepatide is a GIP receptor and GLP-1 receptor agonist. It is a 39-amino-acid modified peptide with a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1. Tirzepatide enhances first- and second-phase insulin secretion, and reduces glucagon levels, both in a glucose-dependent manner.

Mounjaro™ (tirzepatide) indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated, and glucagon secretion is inhibited. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase.

Ozempic®, Rybelsus® (semaglutide) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease.

Dulaglutide is a human GLP-1 receptor agonist. Dulaglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase in pancreatic beta cells. Dulaglutide increases intracellular cyclic AMP (cAMP) in beta cells leading to glucose-dependent insulin release. Dulaglutide also decreases glucagon secretion and slows gastric emptying.
Trulicity® (dulaglutide) is indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus and to reduce the risk of major adverse cardiovascular

events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors.

Liraglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G-protein, Gs, in pancreatic beta cells. Liraglutide increases intracellular cyclic AMP (cAMP) leading to insulin release in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia. Liraglutide also decreases glucagon secretion in a glucose-dependent manner. The mechanism of blood glucose lowering also involves a delay in gastric emptying.

Victoza® is indicated as an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus and to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease.

Lixisenatide is a GLP-1 receptor agonist. Lixisenatide increases glucose-dependent insulin release, decreases glucagon secretion, and slows gastric emptying.

Adlyxin® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Policy:

INITIAL CRITERIA Byetta®, Bydureon®/Bydureon BCise®, Mounjaro™, Ozempic®, Rybelsus®, Trulicity®, Victoza® is approved when ALL of the following are met:

1. ONE of the following:
    a. For members requiring ongoing treatment for type 2 diabetes mellitus, submission of medical records (e.g., chart notes) confirming diagnosis of type 2 diabetes mellitus; or
    b. Submission of medical records (e.g., chart notes) confirming diagnosis of type 2 diabetes mellitus as evidenced by one of the following laboratory values:
        i. A1c greater than or equal to 6.5%; or
        ii. Fasting plasma glucose (FPG) greater than or equal to 126mg/dL; or
        iii. 2-hour plasma glucose (PG) greater than or equal to 200mg/dL during OGTT (oral glucose tolerance test); and
2. Inadequate response or inability to tolerate a minimum of 90-day supply of one of the following generics:
    a. Metformin
    b. Metformin ER
    c. Glipizide-metformin
    d. Glyburide-metformin
    e. Pioglitazone-metformin

Initial authorization duration: 2 years

INITIAL CRITERIA Adlyxin® is approved when ALL of the following are met:

1. ONE of the following:
    a. For members requiring ongoing treatment for type 2 diabetes mellitus, submission of medical records (e.g., chart notes) confirming diagnosis of type 2 diabetes mellitus; or
    b. Submission of medical records (e.g., chart notes) confirming diagnosis of type 2 diabetes mellitus as evidenced by one of the following laboratory values:
        i. A1c greater than or equal to 6.5%; or
        ii. Fasting plasma glucose (FPG) greater than or equal to 126mg/dL; or
        iii. 2-hour plasma glucose (PG) greater than or equal to 200mg/dL during OGTT (oral glucose tolerance test); and
2. Inadequate response or inability to tolerate a minimum of 90-day supply of one of the following generics:
    a. Metformin
    b. Metformin ER
    c. Glipizide-metformin
    d. Glyburide-metformin
    e. Pioglitazone-metformin; and
3. Inadequate response or inability to tolerate a minimum 90-day supply of TWO of the following:
    a. Bydureon/Bydureon BCise
    b. Byetta
    c. Ozempic
    d. Trulicity
    e. Victoza
    f. Rybelsus
    g. Mounjaro

Initial authorization duration: 2 years

REAUTHORIZATION CRITERIA Byetta, Bydureon/Bydureon BCise, Mounjaro, Ozempic, Rybelsus, Trulicity, Victoza, Adlyxin is approved when BOTH of the following are met:

1. Drug is not solely being used for weight loss; and
2. Documentation of positive clinical response to therapy (e.g., reduction in A1c)

Reauthorization duration: 2 years

Black Box Warning as shown in the drug Prescribing Information:

Bydureon®/Bydureon BCise®, Mounjaro™, Ozempic®, Rybelsus®, Trulicity®, Victoza®

WARNING: RISK OF THYROID C-CELL TUMORS

Exenatide extended-release causes thyroid C-cell tumors at clinically relevant exposures in rats. It is unknown whether it causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC) in humans, as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumors has not been determined. It is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and the symptoms of thyroid tumors.

Guidelines:

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the prescription drug benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

References:

Byetta® (exenatide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. December 2022. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=53d03c03-ebf7-418d-88a8-533eabd2ee4f. Accessed June 2, 2023.

Bydureon BCise® (exenatide extended-release) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. December 2022. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2d18cfc4-e0de-4814-a712-c1b7c504bff5. Accessed June 2, 2023.

Mounjaro™ (tirzepatide) [prescribing information]. Indianapolis, IN: Lilly USA, LLC. September 2022. Available from: https://uspl.lilly.com/mounjaro/mounjaro.html#pi. Accessed June 2, 2023.

Ozempic® (semaglutide) [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc. October 2022. Available from: https://www.novo-pi.com/ozempic.pdf. Accessed June 2, 2023.

Rybelsus® (semaglutide) [prescription information]. Plainsboro, NJ: Novo Nordisk Inc. January 2023. Available from: Rybelsus PI (novo-pi.com). Accessed June 2, 2023

Trulicity® (dulaglutide) [prescribing information]. Indianapolis, IN: Eli Lilly and Company. December 2022. Available from: https://uspl.lilly.com/trulicity/trulicity.html#pi. Accessed June 2, 2023.

Victoza® (liraglutide) [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc. July 2022. Available from: https://www.novo-pi.com/victoza.pdf. Accessed June 2, 2023.

Adlyxin® (lixisenatide) [prescribing information]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC. June 2022. Available from: https://products.sanofi.us/Adlyxin/Adlyxin.pdf. Accessed June 2, 2023.

Applicable Drugs:

Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

Brand Name	Generic Name
Byetta®	Exenatide
Bydureon®/Bydureon BCise®	Exenatide extended release
Mounjaro™	Tirzepatide
Ozempic®; Rybelsus®	Semaglutide
Trulicity®	Dulaglutide
Victoza®	Liraglutide
Adlyxin®	Lixisenatide

Cross References:

Rx.01.33 Off Label Use

Rx.01.76 Quantity Level Limits for Pharmaceuticals Covered Under the Prescription Drug Benefit

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