

Clinical Policy: Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

Reference Number: ERX.NPA.137

Effective Date: 03.01.20

Last Review Date: 02.21

Line of Business: Commercial, Medicaid

[Revision Log](#)

See **Important Reminder** at the end of this policy for important regulatory and legal information.

Description

The following agents contain a synthetic glucagon-like peptide-1 (GLP-1) receptor agonist and require prior authorization: dulaglutide (Trulicity®), exenatide ER (Bydureon®, Bydureon® BCise™), exenatide IR (Byetta®), liraglutide (Victoza®), liraglutide/insulin degludec (Xultophy®), lixisenatide (Adlyxin®), lixisenatide/insulin glargine (Soliqua®), and semaglutide (Ozempic®, Rybelsus®).

FDA Approved Indication(s)

GLP-1 receptor agonists are indicated as adjunct to diet and exercise to improve glycemic control with type 2 diabetes mellitus. Victoza is indicated in patients 10 years of age and older, while the other GLP-1 receptor agonists are indicated in adults

Ozempic, Trulicity, and Victoza also are indicated to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and:

- Established cardiovascular disease (*Ozempic, Trulicity, Victoza*);
- Cardiovascular risk factors (*Trulicity only*).

Limitation(s) of use:

- Trulicity, Bydureon, Bydureon BCise, Xultophy, and Rybelsus are not recommended as first-line therapy for patients inadequately controlled on diet and exercise.
- Other than Soliqua and Xultophy which contain insulin, GLP-1 receptor agonists are not a substitute for insulin. They should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis.
- Other than Trulicity, concurrent use with prandial insulin has not been studied and cannot be recommended.
- GLP-1 receptor agonists have not been studied in patients with a history of pancreatitis. Other antidiabetic therapies should be considered.
- Trulicity is not for patients with pre-existing severe gastrointestinal disease.
- Adlyxin has not been studied in patients with gastroparesis and is not recommended in patients with gastroparesis.
- Bydureon and Bydureon BCise are extended-release formulations of exenatide. Do not coadminister with other exenatide containing products.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that GLP-1 receptor agonists are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Type 2 Diabetes Mellitus (must meet all):

1. Diagnosis of type 2 diabetes mellitus;
2. Age is one of the following (a or b):

- a. Victoza: ≥ 10 years;
- b. All other GLP-1 receptor agonists: ≥ 18 years;
3. Member meets one of the following (a or b):
 - a. Failure of ≥ 3 consecutive months of metformin as evidenced by HbA1c $\geq 7\%$, unless contraindicated or clinically significant adverse effects are experienced;
 - b. For medication-naïve members, requested agent is approvable if intended for concurrent use with metformin due to HbA1c $\geq 8.5\%$ (drawn within the past 3 months);
4. If request is for a non-preferred GLP-1 receptor agonist, member meets one of the following (a or b):
 - a. Failure of ≥ 3 consecutive months of a preferred GLP-1 receptor agonist, unless clinically significant adverse effects are experienced or all are contraindicated;
 - b. Member has established cardiovascular disease (e.g., ASCVD) or multiple risk factors for cardiovascular disease (see *Appendix D*), and request is for Ozempic, Trulicity, or Victoza;
5. Dose does not exceed the FDA approved maximum recommended dose (see *Section V*).

Approval duration: 12 months

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Type 2 Diabetes Mellitus (must meet all):

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b):
 - a. Trulicity (i or ii):
 - i. If request is for dose increase from 1.5 mg, new dose does not exceed 3 mg per week (4 vials or pens per month);
 - ii. If request is for dose increase from 3 mg, new dose does not exceed 4.5 mg per week (4 vials or pens per month);
 - b. All other GLP-1 receptor agonists: New dose does not exceed the FDA-approved maximum recommended dose (see *Section V*).

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2):

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.

Approval duration: Duration of request or 12 months (whichever is less); or

2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

- A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AACE: American Association of Clinical Endocrinologists

ACE: American College of Endocrinology

ADA: American Diabetes Association

ASCVD: atherosclerotic cardiovascular disease

ER: extended-release

FDA: Food and Drug Administration

GLP-1: glucagon-like peptide-1

HbA1c: glycated hemoglobin

IR: immediate-release

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
metformin (Fortamet®, Glucophage®, Glucophage® XR, Glumetza®)	<p>Regular-release (Glucophage): 500 mg PO BID or 850 mg PO QD; increase as needed in increments of 500 mg/week or 850 mg every 2 weeks</p> <p>Extended-release:</p> <ul style="list-style-type: none"> Fortamet, Glumetza: 1,000 mg PO QD; increase as needed in increments of 500 mg/week Glucophage XR: 500 mg PO QD; increase as needed in increments of 500 mg/week 	<p>Regular-release: 2,550 mg/day</p> <p>Extended-release: 2,000 mg/day</p>

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
 - Hypersensitivity to any product components
 - Personal or family history of medullary thyroid carcinoma (MTC) and multiple endocrine neoplasia syndrome type 2 (MEN 2) (all GLP-1 receptor agonists other than Adlyxin, Byetta, and Soliqua)
 - Use during episodes of hypoglycemia (Soliqua and Xultophy only)
 - History of drug-induced immune-mediated thrombocytopenia from exenatide products (Bydureon, Bydureon BCise, and Byetta only)
- Boxed warning(s): risk of thyroid C-cell tumors (all agents except Adlyxin, Byetta, and Soliqua)

Appendix D: General Information

- A double-blind, placebo-controlled dose-response trial by Garber et al. found the maximal efficacy of metformin to occur at doses of 2,000 mg. However, the difference in adjusted mean change in HbA1c between the 1500 and 2,000 mg doses was 0.3%, suggesting that the improvement in glycemic control provided by the additional 500 mg may be insufficient when HbA1c is > 7%.
- Per the 2020 American Diabetes Association (ADA) and 2020 American Association of Clinical Endocrinologists and American College of Endocrinology (AAACE/ACE) guidelines:
 - Metformin is recommended for all patients with type 2 diabetes. Monotherapy is recommended for most patients; however:
 - Starting with dual therapy (i.e., metformin plus another agent, such as a sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 inhibitor, sodium-glucose co-transporter inhibitor, GLP-1 receptor agonist, or basal insulin) may be considered for patients with baseline HbA1c ≥ 1.5% above their target per the ADA (≥ 7.5% per the AAACE/ACE). According to the ADA, a reasonable HbA1c target for many non-pregnant adults is < 7% (≤ 6.5% per the AAACE/ACE).
 - Starting with combination therapy with insulin may be considered for patients with baseline HbA1c > 10% per the ADA (> 9% if symptoms are present per the AAACE/ACE).
 - If the target HbA1c is not achieved after approximately 3 months of monotherapy, dual therapy should be initiated. If dual therapy is inadequate after 3 months, triple therapy should be initiated. Finally, if triple therapy fails to bring a patient to goal, combination therapy with insulin should be initiated. Each non-insulin agent added to initial therapy can lower HbA1c by 0.7-1%.
- Although Trulicity is currently the only GLP-1 receptor agonist that is FDA approved for use in patients with multiple cardiovascular risk factors, the 2020 ADA guidelines recognize Ozempic, Trulicity, and Victoza as agents that confer cardiovascular benefit and recommend the use of any

of the three in patients at high risk of ASCVD, without preference for any one over the other. In addition, patients with multiple cardiovascular risk factors were included in each drug's cardiovascular outcomes trial.

- Examples of cardiovascular risk factors may include but are not limited to: dyslipidemia, hypertension, obesity, a family history of premature coronary disease, smoking, chronic kidney disease, and presence of albuminuria.

V. Dosage and Administration

Drug Name	Dosing Regimen	Maximum Dose
Adlyxin (lixisenatide)	Initial dose: 10 mcg SC daily for 14 days Maintenance dose: 20 mcg SC daily	20 mcg/day
Bydureon (exenatide ER)	2 mg SC once weekly	2 mg/week
Bydureon BCise (exenatide ER)	2 mg SC once weekly	2 mg/week
Byetta (exenatide IR)	5 mcg to 10 mcg SC twice daily	20 mcg/day
Ozempic (semaglutide)	0.25 mg to 1 mg SC once weekly	1 mg/week
Rybelsus (semaglutide)	Initial dose: 3 mg PO QD. After 30 days on the 3 mg dose, increase to 7 mg PO QD. May increase to 14 mg PO QD if needed after at least 30 days on the 7 mg dose	14 mg/day
Soliqua (lixisenatide/insulin glargine)	Treatment naïve to basal insulin or GLP-1 receptor agonist, currently on a GLP-1 agonist, or currently on less than 30 units of basal insulin daily: 15 units (15 units insulin/5 mcg lixisenatide) SC QD Currently on 30 to 60 units of basal insulin daily, with or without GLP-1 receptor agonist: 30 units (30 units insulin/10 mcg lixisenatide) SC QD	60 units insulin/20 mcg lixisenatide/day
Trulicity (dulaglutide)	0.75 mg to 1.5 mg SC once weekly. May increase to 3 mg once weekly if needed after at least 4 weeks on 1.5 mg dose. May further increase to 4.5 mg once weekly if needed after at least 4 weeks on 3 mg dose.	4.5 mg/week
Victoza (liraglutide)	Initial: 0.6 mg SC daily for 7 days Maintenance: 1.2 mg to 1.8 mg SC daily	1.8 mg/day
Xultophy (liraglutide/insulin degludec)	Treatment naïve to basal insulin or GLP-1 receptor agonist: 10 units (10 units of insulin/0.36 mg liraglutide) SC QD Treatment experienced to basal insulin or GLP-1 receptor agonist: 16 units (16 units insulin/0.58 mg liraglutide) SC QD	50 units insulin/ 1.8 mg liraglutide/day

VI. Product Availability

Drug Name	Availability
Adlyxin (lixisenatide)	<ul style="list-style-type: none"> • Multi-dose prefilled pen: 50 mcg/mL in 3 mL (14 doses; 10 mcg/dose), 100 mcg/mL in 3 mL (14 doses; 20 mcg/dose)
Bydureon (exenatide ER)	<ul style="list-style-type: none"> • Single-dose tray: 2 mg vial • Single-dose prefilled pen: 2 mg pen
Bydureon BCise (exenatide ER)	<ul style="list-style-type: none"> • Single-dose autoinjector: 2 mg
Byetta (exenatide IR)	<ul style="list-style-type: none"> • Prefilled pen: 5 mcg/dose (0.02 mL) in 1.2 mL (60 doses)

Drug Name	Availability
	<ul style="list-style-type: none"> Prefilled pen: 10 mcg/dose (0.04 mL) in 2.4 mL (60 doses)
Ozempic (semaglutide)	<ul style="list-style-type: none"> Prefilled pen: 2 mg/1.5mL (1.34 mg/mL) for 0.25 mg or 0.5 mg dose; 2 mg/1.5mL (1.34 mg/mL) for 1 mg dose (2 doses per pen); 4 mg/3 mL (1.34 mg/mL) for 1 mg dose (4 doses per pen)
Rybelsus (semaglutide)	<ul style="list-style-type: none"> Tablet: 3 mg, 7 mg, 14 mg
Soliqua (lixisenatide/insulin glargine)	<ul style="list-style-type: none"> Single-patient use pen: 33 mcg/100 units per mL in 3 mL
Trulicity (dulaglutide)	<ul style="list-style-type: none"> Single-dose prefilled pen: 0.75 mg/0.5 mL, 1.5 mg/0.5 mL, 3 mg/0.5 mL, 4.5 mg/0.5 mL
Victoza (liraglutide)	<ul style="list-style-type: none"> Multi-dose prefilled pen: 18 mg/3 mL (6 mg/mL; delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg)
Xultophy (liraglutide/insulin degludec)	<ul style="list-style-type: none"> Single-patient use pen: 3.6 mg/100 units per mL in 3 mL

VII. References

- American Diabetes Association. Standards of medical care in diabetes—2020. Diabetes Care. 2020; 43(suppl 1): S1-S212. Updated June 5, 2020. Accessed October 26, 2020.
- Adlyxin Prescribing Information. Bridgewater, NJ: Sanofi-aventis US LLC; January 2019. Available at: www.adlyxin.com. Accessed October 26, 2020.
- Bydureon Prescribing Information. San Diego, CA: Amylin Pharmaceuticals, Inc; February 2020. Available at: www.bydureon.com. Accessed October 26, 2020.
- Bydureon BCise Prescribing Information. San Diego, CA: Amylin Pharmaceuticals, Inc; February 2020. Available at: www.bydureonbcise.com. Accessed October 26, 2020.
- Byetta Prescribing Information. San Diego, CA: Amylin Pharmaceuticals, Inc; February 2020. Available at: www.byetta.com. Accessed October 26, 2020.
- Soliqua Prescribing Information. Bridgewater, NJ: Sanofi-aventis US LLC; November 2019. Available at: www.soliqua.com. Accessed October 26, 2020.
- Trulicity Prescribing Information. Indianapolis, IN: Eli Lilly and Company, Inc; September 2020. Available at: www.trulicity.com. Accessed October 26, 2020.
- Victoza Prescribing Information. Princeton, NJ: Novo Nordisk Inc; August 2020. Available at: www.victoza.com. Accessed October 26, 2020.
- Xultophy Prescribing Information. Bagsvaerd, Denmark: Novo Nordisk A/S; November 2019. Available at: www.xultophy.com. Accessed October 26, 2020.
- Garber AJ, Duncan TG, Goodman AM, et al. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. Am J Med. 1997; 102: 491-497.
- Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2020 executive summary. Endocr Pract. 2020; 26(1): 107-139.
- Ozempic Prescribing Information. Bagsvaerd, Denmark: Novo Nordisk A/S; September 2020. Available at: www.ozempic.com. Accessed October 26, 2020.
- Rybelsus Prescribing Information. Bagsvaerd, Denmark: Novo Nordisk A/S; January 2020. Available at: www.rybelsuspro.com. Accessed October 26, 2020.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created: adapted from ERX.ST.34 GLP-1 receptor agonists; added diagnosis, age, and positive response requirements; clarified that failure of metformin must be evidenced by HbA1c at least 7%; references reviewed and updated.	10.29.19	02.20
RT4: added new Ozempic cardiovascular risk reduction indication; removed first-line therapy limitation of use for Ozempic, Victoza, Byetta, Soliqua, and Adlyxin.	01.30.20	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
"FDA Approved Indications" section updated to include Trulicity's new FDA indication: cardiovascular risk reduction in patients with established cardiovascular disease or with multiple cardiovascular risk factors; criteria modified to allow Ozempic, Trulicity, and Victoza in patients with established cardiovascular disease or risk factors; added new exenatide contraindication to Appendix C; references reviewed and updated.	04.07.20	08.20
RT4: added new dosage strength (3 mg, 4.5 mg) forms for Trulicity	09.29.20	
1Q 2021 annual review: no significant changes; added new dosage strength (4 mg/3 mL) form for Ozempic; references reviewed and updated.	10.26.20	02.21

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

This policy is the property of Envolve Pharmacy Solutions. Unauthorized copying, use, and distribution of this Policy or any information contained herein is strictly prohibited. By accessing this policy, you agree to be bound by the foregoing terms and conditions, in addition to the Site Use Agreement for Health Plans associated with Envolve Pharmacy Solutions.

©2020 Envolve Pharmacy Solutions. All rights reserved. All materials are exclusively owned by Envolve Pharmacy Solutions and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Envolve Pharmacy Solutions. You may not alter or remove any trademark, copyright or other notice contained herein.