

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

Reference Number: CP.PMN.183

Effective Date: 09.19.18

Last Review Date: 02.21

Line of Business: 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 are also 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 a 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.

It is the policy of health plans affiliated with Centene Corporation[®] 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 $\text{HbA1c} \geq 7\%$, 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 $\text{HbA1c} \geq 8.5\%$ (drawn within the past 3 months);
4. Failure of ≥ 3 consecutive month trial of a sodium-glucose co-transporter 2 (SGLT2) inhibitor or SGLT2-containing product (see *Appendix B*), unless clinically significant adverse effects are experienced or all are contraindicated;
5. If request is for a non-preferred GLP-1 receptor agonist, failure of ≥ 3 consecutive months of a preferred GLP-1 receptor agonist (e.g., Victoza, Bydureon, Bydureon BCise, Byetta), unless (a or b):
 - a. Clinically significant adverse effects are experienced or all are contraindicated;
 - b. Request is for Ozempic or Trulicity, member has established cardiovascular disease (e.g., ASCVD) or multiple cardiovascular risk factors, and Victoza is contraindicated;
6. Dose does not exceed the FDA-approved maximum recommended dose (see *Section V*).

Approval duration: 12 months

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, 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 Centene benefit and documentation supports positive response to therapy.

- Approval duration: Duration of request or 12 months (whichever is less); or**
- Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid.

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

- 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 policies – CP.PMN.53 for Medicaid 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 for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
metformin (Fortamet [®] , Glucophage [®] , Glucophage XR, Glumetza [®])	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 Extended-release: <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 	Regular-release: 2,550 mg/day Extended-release: 2,000 mg/day
SGLT2 Inhibitors		
Farxiga [®] (dapagliflozin)	5 mg PO QD To reduce the risk of hospitalization for heart failure, the recommended dose is 10 mg PO QD	10 mg/day
Glyxambi [®] (empagliflozin/linagliptin)	One 10/5 mg tablet PO QD	25/5 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Invokamet [®] (canagliflozin/metformin)	One 50/500 mg tablet PO BID	300/2,000 mg/day
Invokamet [®] XR (canagliflozin/metformin)	Two 50/500 mg tablets PO QD	300/2,000 mg/day
Invokana [®] (canagliflozin)	100 mg PO QD	300 mg/day
Jardiance [®] (empagliflozin)	10 mg PO QD	25 mg/day
Qtern [®] (dapagliflozin/saxagliptin)	One 5/5 mg tablet PO QD	10/5 mg/day
Qternmet [®] XR (dapagliflozin/saxagliptin/m etformin)	Individualized dose PO QD	10/5/2,000 mg/day
Steglujan [™] (ertugliflozin/sitagliptin)	One 5/100 mg tablet PO QD	15/100 mg/day
Synjardy [®] (empagliflozin/metformin)	Individualized dose PO BID	25/2,000 mg/day
Synjardy [®] XR (empagliflozin/metformin)	Individualized dose PO QD	25/2,000 mg/day
Trijardy [™] XR (empagliflozin/linagliptin/ metformin)	Individualized dose PO QD	25/5/2,000 mg/day
Xigduo [®] XR (dapagliflozin/metformin)	Individualized dose PO QD	10/2,000 mg/day

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 or multiple endocrine neoplasia syndrome type 2 (*all GLP-1 receptor agonists other than Byetta, Adlyxin, 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): thyroid C-cell tumors (*all GLP-1 receptor agonists other than Byetta, Adlyxin, 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 1,500 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 (AACE/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 $\geq 1.5\%$ above their target per the ADA ($\geq 7.5\%$ per the AACE/ACE). According to the ADA, a reasonable HbA1c target for many non-pregnant adults is $< 7\%$ ($\leq 6.5\%$ per the AACE/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 AACE/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 QD for 14 days Maintenance dose: 20 mcg SC QD	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 BID	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 receptor agonist, or currently on	60 units insulin/20 mcg lixisenatide/day

Drug Name	Dosing Regimen	Maximum Dose
	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	
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 QD for 7 days Maintenance: 1.2 mg to 1.8 mg SC QD	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)	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)	Single-dose autoinjector: 2 mg
Byetta (exenatide IR)	Prefilled pen: 5 mcg/dose (0.02 mL) in 1.2 mL (60 doses), 10 mcg/dose (0.04 mL) in 2.4 mL (60 doses)
Ozempic (semaglutide)	Prefilled pen: 2 mg/1.5 mL (1.34 mg/mL) for 0.25 mg or 0.5 mg dose; 2 mg/1.5 mL (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)	Tablet: 3 mg, 7 mg, 14 mg
Soliqua (lixisenatide/insulin glargine)	Single-patient use pen: 33 mcg/100 units per mL in 3 mL
Trulicity (dulaglutide)	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)	Multi-dose prefilled pen: 18 mg/3 mL (6 mg/mL; delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg)

Drug Name	Availability
Xultophy (liraglutide/insulin degludec)	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. Wilmington, DE: AstraZeneca Pharmaceuticals, LP; February 2020. Available at: www.bydureon.com. Accessed October 26, 2020.
- Bydureon BCise Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals, LP; February 2020. Available at: www.bydureonbcise.com. Accessed October 26, 2020.
- Byetta Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals, LP; 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
1Q 2019 Policy created: adapted from previously approved corporate policy CP.PST.14; modified to reflect that all GLP-1 receptor agonists now require PA (instead of ST) and added diagnosis per SDC chair; removed Tanzeum as GlaxoSmithKline discontinued its manufacturing/sale in July 2018; modified minimum A1c related for concurrent use of metformin from 9% to	09.19.18	02.19

Reviews, Revisions, and Approvals	Date	P&T Approval Date
8.5% based on 2019 ADA guidelines; references reviewed and updated.		
No significant changes; updated FDA approved indications for Soliqua and Xultophy to remove requirement for failure of basal insulin and corresponding GLP-1 receptor agonists, lixisenatide and liraglutide respectively; updated dosage and administration for treatment naïve patients; references reviewed and updated.	03.12.19	
Clarified that failure of metformin must be evidenced by HbA1c at least 7%.	04.22.19	05.19
RT4: updated criteria to reflect Victoza's pediatric expansion to ages 10 and older.	06.25.19	
Added new oral semaglutide formulation, Rybelsus; references reviewed and updated.	10.17.19	11.19
1Q 2020 annual review: no significant changes; references reviewed and updated.	10.29.19	02.20
For Rybelsus requests, added requirement for trial of a SGLT2 inhibitor per SDC and prior clinical guidance; RT4: added new Ozempic cardiovascular risk reduction indication; removed first-line therapy limitation of use for Ozempic, Victoza, Byetta, Soliqua, and Adlyxin.	03.05.20	
Updated "FDA Approved Indications" section to include Trulicity's new FDA indication: cardiovascular risk reduction in patients with established cardiovascular disease or with multiple cardiovascular risk factors; modified criteria to allow Trulicity or Ozempic in patients with established cardiovascular disease or multiple cardiovascular risk factors if contraindicated to the preferred agent Victoza; 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	
Per December SDC and prior clinical guidance, required redirection to SGLT2-containing product for ALL GLP-1 requests, not just Rybelsus.	12.15.20	
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
Removed Trulicity step-wise dose escalation criteria based on cost/PA analysis and low anticipation for inappropriate usage.	03.11.21	

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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 clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:

For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

©2018 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation 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 Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene[®] and Centene Corporation[®] are registered trademarks exclusively owned by Centene Corporation.