

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

Reference Number: CP.CPA.16

Effective Date: 11.16.16

Last Review Date: 02.22

Line of Business: Commercial

[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[®]), 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. Bydureon, Bydureon BCise, and Victoza are 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:

- Bydureon, Bydureon BCise, Xultophy, and Rybelsus are not recommended as a first-line therapy for patients inadequately controlled on diet and exercise.
- GLP-1 receptor agonists should not be used for the treatment of type 1 diabetes. Xultophy and Soliqua are not for the treatment of diabetic ketoacidosis.
- Xultophy and Soliqua have not been studied in combination with prandial insulin. In addition, they are not recommended for use in combination with any other product containing a GLP-1 receptor agonist.
- Other than Victoza and Xultophy, 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 and Soliqua are not recommended in patients with gastroparesis.
- Bydureon and Bydureon BCise are extended-release formulations of exenatide. Do not coadminister with other exenatide containing products.
- Victoza and Xultophy contain liraglutide and should not be co-administered with other liraglutide-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. Bydureon, Bydureon BCise, 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 antidiabetic 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 Adlyxin, Bydureon, Byetta, Soliqua, Tanzeum, or Xultophy: Failure of ≥ 3 consecutive months of all of the following, unless clinically significant adverse effects are experienced or all are contraindicated: Victoza, Trulicity, Ozempic;
5. If request is for Rybelsus: Failure of a sodium-glucose co-transporter 2 (SGLT2) inhibitor (see *Appendix B*), unless clinically significant adverse effects are experienced or all are contraindicated;
6. Dose does not exceed one of the following:
 - a. Adlyxin: 20 mcg per day (2 pens per month);
 - b. Bydureon: 2 mg per week (4 vials or pens per month);
 - c. Byetta: 20 mcg per day (4 vials or pens per month);
 - d. Ozempic: 2 mg per week (1 pen per month);
 - e. Rybelsus: 14 mg per day (1 tablet per day);
 - f. Soliqua: 60 units/20 mcg per day (6 pens per month);
 - g. Trulicity: 4.5 mg per week (4 vials or pens per month);
 - h. Victoza: 1.8 mg per day (4 vials or pens per month);
 - i. Xultophy: 50 units/1.8 mg per day (6 pens per month).

Approval duration:

Rybelsus – 12 months

All other agents – 6 months or member's renewal period, whichever is longer

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.CPA.09 for commercial.

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 one of the following:
 - a. Adlyxin: 20 mcg per day (2 pens per month);
 - b. Bydureon: 2 mg per week (4 vials or pens per month);
 - c. Byetta: 20 mcg per day (4 vials or pens per month);
 - d. Ozempic: 2 mg per week (1 pen per month);
 - e. Rybelsus: 14 mg per day (1 tablet per day);
 - f. Soliqua: 60 units/20 mcg per day (6 pens per month);
 - g. Trulicity: 4.5 mg per week (4 vials or pens per month);
 - h. Victoza: 1.8 mg per day (4 vials or pens per month);
 - i. Xultophy: 50 units/1.8 mg per day (6 pens per month).

Approval duration:

Rybelsus – 12 months

All other agents – 6 months or member’s renewal period, whichever is longer

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

2. 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.CPA.09 for commercial.

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 – CP.CPA.09 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

CVD: cardiovascular disease

ER: extended-release

FDA: Food and Drug Administration

GLP-1: glucagon-like peptide-1

HbA1c: glycated hemoglobin

IR: immediate-release

MEN 2: multiple endocrine neoplasia syndrome type 2

MTC: medullary thyroid carcinoma

SGLT2: sodium-glucose co-transporter 2

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.

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Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
metformin (Glucophage [®] , Glucophage [®] XR, Fortamet ^{®*} , 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
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
Segluromet [™] (ertugliflozin/metformin)	Individualized dose PO BID	15/2,000 mg/day
Steglatro [™] (ertugliflozin)	5 mg PO QD	15 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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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.

**Fortamet and Glumetza are non-formulary products.*

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

- Per the American Diabetes Association (ADA) and 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 \geq 1.5% above their target per the ADA (\geq 7.5% per the AAACE/ACE). According to the ADA, a reasonable HbA1c target for many non-pregnant adults is $<$ 7% (\leq 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%.
- Not approvable for appetite suppression or treatment of obesity since currently there are no studies to support the use of Byetta, Tanzeum, Trulicity, or Victoza for these conditions.

V. Dosage and Administration

Drug Name	Dosing Regimen	Maximum Dose
Adlyxin (lixisenatide)	Initial dose: 10 mcg SC QD for 14 days	20 mcg/day

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Drug Name	Dosing Regimen	Maximum Dose
	Maintenance dose: 20 mcg SC QD	
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 2 mg SC once weekly, increased no more frequently than every 4 weeks	2 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 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 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

Drug Name	Availability
	<ul style="list-style-type: none"> 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 dose (4 doses of 0.25 mg and 2 doses of 0.5 mg per pen) or 0.5 mg dose (4 doses per pen); 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); 8 mg/3 mL (2.68 mg/mL) for 2 mg dose (4 doses per pen)
Rybelsus (semaglutide)	Tablets: 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)
Xultophy (liraglutide/insulin degludec)	Single-patient use pen: 3.6 mg/100 units per mL in 3 mL

VII. References

1. Bydureon Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals, LP; July 2021. Available at: www.bydureon.com. Accessed September 16, 2021.
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4. Trulicity Prescribing Information. Indianapolis, IN: Eli Lilly and Company, Inc; April 2021. Available at: www.trulicity.com. Accessed September 16, 2021.
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7. 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.
8. Adlyxin Prescribing Information. Bridgewater, NJ: Sanofi-aventis US LLC; July 2021. Available at: www.adlyxin.com. Accessed September 16, 2021.
9. Soliqua Prescribing Information. Bridgewater, NJ: Sanofi-aventis US LLC; July 2021. Available at: www.soliqua.com. Accessed September 16, 2021.

10. Xultophy Prescribing Information. Bagsvaerd, Denmark: Novo Nordisk A/S; November 2019. Available at: www.xultophy.com. Accessed September 16, 2021.
11. Ozempic Prescribing Information. Bagsvaerd, Denmark: Novo Nordisk A/S; March 2022. Available at: www.ozempic.com. Accessed April 13, 2022.
12. Rybelsus Prescribing Information. Bagsvaerd, Denmark: Novo Nordisk A/S; April 2021. Available at: www.rybelsuspro.com. Accessed September 16, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q18 annual review: Removed requirement for documentation of baseline A1c as this does not dictate coverage decision; Added option for members with A1c \geq 9% to bypass previous use of metformin for 3 months per ADA guidelines (concurrent metformin use is still required); Removed requirement for concurrent use of metformin on re-auth; References reviewed and updated.	11.30.17	02.18
Added Ozempic to criteria.	03.22.18	05.18
No significant changes: removed redirection to Victoza and Trulicity for Ozempic per SDC	08.01.18	
1Q 2019 annual review: added age \geq 18 years; clarified metformin trial required to be consecutive months; modified minimum A1c related for concurrent use of metformin from 9% to 8.5% based on 2019 ADA guidelines; removed medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 exclusions from Section III; removed Tanzeum as GlaxoSmithKline discontinued its manufacturing/sale in July 2018; initial approval duration modified to length of benefit; references reviewed and updated.	10.12.18	02.19
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	
Revised approval durations from length of benefit to 12 months.	10.16.19	
Added new oral semaglutide formulation, Rybelsus; references reviewed and updated.	10.17.19	11.19
Revised approval durations for injectable agents from 12 months to “6 months or member’s renewal period, whichever is longer.”	11.22.19	
1Q 2020 annual review: no significant changes; references reviewed and updated.	11.23.19	02.20
For Rybelsus requests, added requirement for trial of a SGLT2 inhibitor per SDC and prior clinical guidance; RT4: added new	03.05.20	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Ozempic cardiovascular risk reduction indication; removed first-line therapy limitation of use for Ozempic, Victoza, Byetta, Soliqua, and Adlyxin.		
“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; added new exenatide contraindication to Appendix C; references reviewed and updated.	04.07.20	08.20
Per October SDC and prior clinical guidance, modified redirection to require a 3 month trial each of Victoza, Trulicity, and Ozempic for Adlyxin, Bydureon, Byetta, Soliqua, Tanzeum, and Xultophy; RT4: added new dosage strength (3 mg, 4.5 mg) forms for Trulicity	10.07.20	
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	
Added Steglatro and Segluromet to Appendix B.	04.09.21	
RT4: updated indication and age limits down to 10 years of age for Bydureon and Bydureon BCise per updated prescribing information.	08.03.21	
1Q 2022 annual review: no significant changes; references reviewed and updated.	09.16.21	02.22
RT4: added new dosage strength (2 mg) form for Ozempic.	04.13.22	

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,

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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.

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