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

Reference Number: CP.PMN.183
Effective Date: 09.19.18
Last Review Date: 02.22
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®), semaglutide (Ozempic®, Rybelsus®), and tirzepatide* (Mounjaro™).
**Tirzepatide is a combination GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist.*

Requests for Soliqua® (lixisenatide/insulin glargine) should be reviewed against CP.PST.01 – Step Therapy Criteria.

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 is not for the treatment of diabetic ketoacidosis.
- Xultophy has 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 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.
- 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 ≥ 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 ≥ 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 inhibitor-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., Bydureon, Bydureon BCise, Byetta), unless (a or b):
   a. Clinically significant adverse effects are experienced or all are contraindicated;
   b. Request is for Ozempic, Trulicity, or Victoza, and member has established cardiovascular disease (e.g., ASCVD) or multiple cardiovascular risk factors;
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
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.PMN.53 for Medicaid.

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 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
GIP: glucose-dependent insulinotropic polypeptide
GLP-1: glucagon-like peptide-1
HbA1c: glycated hemoglobin
IR: immediate-release
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 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: • 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	10 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	To reduce the risk of hospitalization for heart failure, the recommended dose is 10 mg PO QD	
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
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, and Adlyxin*)
  - Use during episodes of hypoglycemia (*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, and Adlyxin*)

Appendix D: General Information

- Per the American Diabetes Association (ADA) and 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 ≥ 1.5% above their target per the ADA (≥ 7.5% per the AACE/ACE). According to the ADA, a reasonable HbA1c target for many non-pregnant adults is < 7% (≤ 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 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.
- According to the ADA, ASCVD includes coronary heart disease, cerebrovascular disease, or peripheral arterial disease presumed to be of atherosclerotic origin. Indicators of high ASCVD risk are age ≥ 65 years with coronary, carotid, or lower-extremity artery stenosis > 50% or left ventricular hypertrophy.

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
Mounjaro (tirzepatide)	Initial dose: 2.5 mg SC once weekly. May increase by 2.5 mg every 4 weeks up to 15 mg once weekly	15 mg/week

Drug Name	Dosing Regimen	Maximum Dose
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
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)	• 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)
Mounjaro (tirzepatide)	Single-dose prefilled pen: 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, 15 mg/0.5 mL
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

Drug Name	Availability
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

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6. 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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8. Xultophy Prescribing Information. Bagsvaerd, Denmark: Novo Nordisk A/S; November 2019. Available at: www.xultophy.com. Accessed September 16, 2021.
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10. Ozempic Prescribing Information. Bagsvaerd, Denmark: Novo Nordisk A/S; March 2022. Available at: www.ozempic.com. Accessed April 13, 2022.
11. Rybelsus Prescribing Information. Bagsvaerd, Denmark: Novo Nordisk A/S; April 2021. Available at: www.rybelsuspro.com. Accessed September 16, 2021.
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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	09.19.18	02.19

Reviews, Revisions, and Approvals	Date	P&T Approval Date
concurrent use of metformin from 9% to 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	
Per March SDC, removed Victoza as a preferred agent.	03.09.21	05.21
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: per November SDC removed Soliqua from criteria and added reference to CP.PST.01 step therapy criteria for	11.30.21	02.22

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Soliqua requests; WCG.CP.PMN.183 to be retired; references reviewed and updated.		
RT4: added new dosage strength (2 mg) form for Ozempic.	04.13.22	
RT4: added newly FDA approved drug, Mounjaro.	05.31.22	

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, 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.