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

Reference Number: MDN.CP.PMN.183
Effective Date: 8.1.23
Last Review Date: 5.23.24
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 BCise®), exenatide IR (Byetta®), liraglutide (Victoza®), liraglutide/insulin degludec (Xultophy®), lixisenatide (Adlyxin®), semaglutide (Ozempic®, Rybelsus®), tirzepatide* (Mounjaro™), insulin glargine/ lixisenatide (Soliqua®).

**Tirzepatide is a combination GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist.*

## 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 BCise, Trulicity, 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 BCise, and Xultophy 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 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. If the request is for Rybelsus, Trulicity or Victoza;
   a. Diagnosis of Type 2 Diabetes mellitus only- all other indications should be denied;
2. Diagnosis of type 2 diabetes mellitus;
3. Age is one of the following (a or b):
   a. Bydureon BCise, Trulicity, Victoza: ≥ 10 years ;
   b. All other GLP-1 receptor agonists: ≥ 18 years;
4. If request is for Rybelsus, member meets one of the following (a or b):
   a. Failure of ≥ 3 consecutive months of metformin at maximum indicated dose as evidenced by HbA1c ≥ 7%, unless contraindicated or clinically significant adverse effects are experienced;
   b. HbA1c drawn within the past 3 months is ≥ 8.5%, and concurrent use of metformin unless contraindicated or clinically significant adverse effects are experienced;
5. Member meets one of the following (a or b):
   a. If request is for Ozempic and member has established cardiovascular disease (e.g., ASCVD) or multiple cardiovascular risk factors *(see Appendix D)*: Failure of ≥ 3 consecutive months of Trulicity or Victoza, unless clinically significant adverse effects are experienced or all are contraindicated;
   b. 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., Rybelsus Trulicity, Victoza) unless clinically significant adverse effects are experienced or all are contraindicated;
6. If request is for Soliqua, member meets the following (a and b):
   a. Prescribed a Basal insulin within the past 180 days (*see Appendix B*);
   b. Failure of ≥ 3 consecutive months of Trulicity or Victoza;
7. Request product is not prescribed concurrently with another GLP-1 receptor agonist;
8. If request is for Wegovy see MDN.CP.PMN.295;
9. 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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):

a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.
3. Weight loss is a benefit exclusion and is not a covered benefit.

**II. Continued Therapy**

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

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy;
3. Request product is not prescribed concurrently with another GLP-1 receptor agonist;
4. 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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.
3. Weight loss is a benefit exclusion and is not a covered benefit.
4.

**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
GLP-1: glucagon-like peptide-1
HbA1c: glycated hemoglobin
IR: immediate-release
SGLT2: sodium-glucose co-transporter 2
GIP: glucose-dependent insulinotropic polypeptide

*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<br><br>Extended-release:<br>• Fortamet, Glumetza: 1,000 mg PO QD; increase as needed in increments of 500 mg/week<br>• Glucophage XR: 500 mg PO QD; increase as needed in increments of 500 mg/week | Regular-release: 2,550 mg/day<br><br>Extended-release: 2,000 mg/day |
| **SGLT2 Inhibitors** | | |
| Farxiga® (dapagliflozin) | 5 mg PO QD<br><br>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 |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| 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/metformin) | 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 (*Xultophy and Soliqua only*)
  - History of drug-induced immune-mediated thrombocytopenia from exenatide products (*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 (AACE/ACE) guidelines:
  - Metformin is recommended for all patients with type 2 diabetes. It is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death. Monotherapy is recommended for most patients; however:
    - Starting with dual therapy (i.e., metformin plus another agent, such as a SU, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin) may be considered for patients with baseline HbA1c ≥ 1.5% above their target. 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% or if symptoms of hyperglycemia are present.
        - For patients with established ASCVD or indicators of high ASCVD risk, heart failure, or chronic kidney disease, use of an SGLT2 inhibitor or GLP-1 receptor agonist with demonstrated cardiovascular benefit is recommended as part of the glucose-lowering regimen independent of HbA1c and metformin use.
    - 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 ≥ 55 years with coronary, carotid, or lower-extremity artery stenosis > 50%; left ventricular hypertrophy; retinopathy; and other end organ damage.

## V. Dosage and Administration

| | | |
|---|---|---|
| Adlyxin (lixisenatide) | Initial dose: 10 mcg SC QD for 14 days<br>Maintenance dose: 20 mcg SC QD | 20 mcg/day |
| 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 |
| 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 | 60 units insulin/20 mcg lixisenatide/day |

| | | |
|---|---|---|
| | less than 30 units of basal insulin daily: 15 units (15 units insulin/5 mcg lixisenatide) SC QD<br>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<br>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<br><br>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 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:<br>• 2 mg/3 mL (0.68 mg/mL); delivers 0.25 mg or 0.5 mg per injection<br>• 4 mg/3 mL (1.34 mg/mL); delivers 1 mg per injection<br>8 mg/3 mL (2.68 mg/mL); delivers 2 mg per injection |
| 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 |

| Drug Name | Availability |
|---|---|
| Victoza (liraglutide) | Multi-dose prefilled pen: 6 mg/mL in 3 mL (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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| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| Policy created, adapted from IL.PMN.183 | 7.6.23 | |
| 2Q 2024 annual review: clarified initial approval criteria ; for Ozempic, removed 2 mg/1.5 mL (1.34 mg/mL) from section VI as strength is not currently marketed; removed Bydureon as no longer available; updated Appendix C updated Appendix D; references reviewed and updated. | 5.23.24 | |

**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.

**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.