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

Reference Number: CP.PMN.183
Effective Date: 09.19.18
Last Review Date: 02.20
Line of Business: Medicaid

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 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.

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 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;
   4. If request is for a non-preferred GLP-1 receptor agonist, failure of ≥ 3
      consecutive months of a preferred GLP-1 receptor agonist, unless clinically
      significant adverse effects are experienced or all are contraindicated;
   5. If request is for Rybelsus, failure of a preferred 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 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
   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.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/ Maximum Dose</th>
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</thead>
</table>
| 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:
  |                                           | Extended-release: 2,000 mg/day |
| Farxiga® (dapagliflozin)       | 5 mg PO QD                                                                    | 10 mg/day                 |
|                               | To reduce the risk of hospitalization for heart failure, the recommended dose is
 | 10 mg PO QD                    | 25/5 mg/day                  |
| Glyxambi® (empagliflozin/linagliptin) | One 10/5 mg tablet PO QD                                                   | 300/2,000 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                |
### Drug Name | Dosing Regimen | Dose Limit/Maximum Dose
--- | --- | ---
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 (Soliqua and Xultophy 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 2019 American Diabetes Association (ADA) and 2019 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 injectable therapy (i.e., with GLP-1 receptor agonist or insulin) may be considered for patients with baseline HbA1c ≥ 10% or ≥ 2% above their target 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 injectable therapy should be initiated. Each non-insulin agent added to initial therapy can lower HbA1c by 0.7-1%.

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adlyxin (lixisenatide)</td>
<td>Initial dose: 10 mcg SC QD for 14 days Maintenance dose: 20 mcg SC QD</td>
<td>20 mcg/day</td>
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<tr>
<td>Bydureon (exenatide ER)</td>
<td>2 mg SC once weekly</td>
<td>2 mg/week</td>
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<tr>
<td>Bydureon BCise (exenatide ER)</td>
<td>2 mg SC once weekly</td>
<td>2 mg/week</td>
</tr>
<tr>
<td>Byetta (exenatide IR)</td>
<td>5 mcg to 10 mcg SC BID</td>
<td>20 mcg/day</td>
</tr>
<tr>
<td>Ozempic (semaglutide)</td>
<td>0.25 mg to 1 mg SC once weekly</td>
<td>1 mg/week</td>
</tr>
<tr>
<td>Rybelsus (semaglutide)</td>
<td>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</td>
<td>14 mg/day</td>
</tr>
<tr>
<td>Soliqua (lixisenatide/insulin glargine)</td>
<td>Treatment naïve to basal insulin or GLP-1 receptor agonist, currently on a GLP-1 receptor agonist, currently on less than 30 units of basal insulin daily: 15 units (15 units insulin/5 mcg lixisenatide) SC QD</td>
<td>60 units insulin/20 mcg lixisenatide/day</td>
</tr>
<tr>
<td></td>
<td>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</td>
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<tr>
<td></td>
<td>Trulicity (dulaglutide)</td>
<td>0.75 mg to 1.5 mg SC once weekly</td>
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<tr>
<td></td>
<td>0.75 mg to 1.5 mg SC once weekly</td>
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<tr>
<td></td>
<td>1.5 mg/week</td>
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<tr>
<td></td>
<td>Victoza (liraglutide)</td>
<td>Initial: 0.6 mg SC QD for 7 days</td>
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<td>Maintenance: 1.2 mg to 1.8 mg SC QD</td>
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<tr>
<td></td>
<td>Xultophy (liraglutide/insulin degludec)</td>
<td>Treatment naïve to basal insulin or GLP-1 receptor agonist: 10 units (10 units of insulin/0.36 mg liraglutide) SC QD</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Dosing Regimen</td>
<td>Maximum Dose</td>
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<tr>
<td></td>
<td>Treatment experienced to basal insulin or GLP-1 receptor agonist: 16 units (16 units insulin/0.58 mg liraglutide) SC QD</td>
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VI. Product Availability

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adlyxin (lixisenatide)</td>
<td>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)</td>
</tr>
</tbody>
</table>
| 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) |
| Ozempic (semaglutide) | 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 |
| 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/0.5mL and 1.5 mg/0.5mL |
| 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


<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
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<tbody>
<tr>
<td>Date</td>
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<td>09.19.18</td>
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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 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

**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.