Clinical Policy: Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists
Reference Number: ERX.ST.34
Effective Date: 03.01.18
Last Review Date: 02.19

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 step therapy: 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®).

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.

Victoza is 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:
- GLP-1 receptor agonists 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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that GLP-1 receptor agonists are medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Step Therapy for GLP-1 Receptor Agonists (must meet all):
      1. Member meets one of the following (a or b):
         a. Previous use of ≥ 3 consecutive months of metformin 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;
2. If request is for a non-preferred GLP-1 receptor agonist, previous use of ≥ 3 consecutive months of a preferred GLP-1 receptor agonist, unless contraindicated or clinically significant adverse effects are experienced;
3. Dose does not exceed the FDA approved maximum recommended dose (see Section V).
**Approval duration: 12 months**

**B. Other diagnoses/indications:** Not applicable

**II. Continued Therapy**

**A. Step Therapy for GLP-1 Receptor Agonists** (must meet all):
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. 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:** Not applicable

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

**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
- Soliqua
- Xultophy

**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.*

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>metformin (Fortamet®, Glucophage®, Glucophage® XR, Glumetza®)</td>
<td>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&lt;br&gt;Extended-release:&lt;br&gt;• Fortamet, Glumetza: 1,000 mg PO QD; increase as needed in increments of 500 mg/week&lt;br&gt;• Glucophage XR: 500 mg PO QD; increase as needed in increments of 500 mg/week</td>
<td>Regular-release: 2,550 mg/day&lt;br&gt;Extended-release&lt;br&gt;• Fortamet: 2,500 mg/day&lt;br&gt;• Glucophage XR, Glumetza: 2,000 mg/day</td>
</tr>
</tbody>
</table>

*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 (MTC) and multiple endocrine neoplasia syndrome type 2 (MEN 2) (all GLP-1 receptor agonists other than Adlyxin, Byetta, and Soliqua)
  - Use during episodes of hypoglycemia (Soliqua and Xultophy only)
- Boxed warning(s): risk of thyroid C-cell tumors (all agents except Adlyxin, Byetta, 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 1500 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 2017 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%.
    - 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 daily for 14 days Maintenance dose: 20 mcg SC daily</td>
<td>20 mcg/day</td>
</tr>
<tr>
<td>Bydureon (exenatide ER)</td>
<td>2 mg SC once weekly</td>
<td>2 mg/week</td>
</tr>
<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 twice daily</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>Soliqua (lixisenatide/insulin</td>
<td>Treatment naïve to basal insulin or GLP-1 receptor agonist, currently on a</td>
<td>60 units insulin/20</td>
</tr>
<tr>
<td>glargine)</td>
<td>GLP-1 agonist, or currently on less than 30 units of basal insulin daily:</td>
<td>mcg lixisenatide/day</td>
</tr>
<tr>
<td></td>
<td>15 units (15 units insulin/5 mcg lixisenatide) SC QD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Currently on 30 to 60 units of basal insulin daily, with or without GLP-1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>receptor agonist: 30 units (30 units insulin/10 mcg lixisenatide) SC QD</td>
<td></td>
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<tr>
<td>Trulicity (dulaglutide)</td>
<td>0.75 mg to 1.5 mg SC once weekly</td>
<td>1.5 mg/week</td>
</tr>
<tr>
<td>Victoza (liraglutide)</td>
<td>Initial: 0.6 mg SC daily for 7 days Maintenance: 1.2 mg to 1.8 mg SC daily</td>
<td>1.8 mg/day</td>
</tr>
<tr>
<td>Xultophy (liraglutide/insulin</td>
<td>Treatment naïve to basal insulin or GLP-1 receptor agonist: 10 units (10</td>
<td>50 units insulin/1.8</td>
</tr>
<tr>
<td>degludec)</td>
<td>units of insulin/0.36 mg liraglutide) SC QD</td>
<td>mg liraglutide/day</td>
</tr>
<tr>
<td></td>
<td>Treatment experienced to basal insulin or GLP-1 receptor agonist: 16 units</td>
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<tr>
<td></td>
<td>(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>
<tr>
<td>Bydureon (exenatide ER)</td>
<td>• Single-dose tray: 2 mg vial</td>
</tr>
<tr>
<td>Bydureon BCise (exenatide ER)</td>
<td>• Single-dose autoinjector: 2 mg</td>
</tr>
<tr>
<td>Byetta (exenatide IR)</td>
<td>• Prefilled pen: 5 mcg/dose (0.02 mL) in 1.2 mL (60 doses)</td>
</tr>
<tr>
<td>Ozempic (semaglutide)</td>
<td>• 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</td>
</tr>
<tr>
<td>Soliqua (lixisenatide/insulin glargine)</td>
<td>• Single-patient use pen: 33 mcg/100 units per mL in 3 mL</td>
</tr>
<tr>
<td>Trulicity (dulaglutide)</td>
<td>• Single-dose prefilled pen: 0.75 mg/0.5mL and 1.5 mg/0.5mL</td>
</tr>
<tr>
<td>Victoza (liraglutide)</td>
<td>• Multi-dose prefilled pen: 6 mg/mL in 3 mL (doses of 0.6 mg, 1.2 mg, or 1.8 mg)</td>
</tr>
<tr>
<td>Xultophy (liraglutide/insulin degludec)</td>
<td>• Single-patient use pen: 3.6 mg/100 units per mL in 3 mL</td>
</tr>
</tbody>
</table>

VII. References
## Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Description</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
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<tbody>
<tr>
<td>modified minimum A1c related for concurrent use of metformin from 9% to 8.5% based on 2019 ADA guidelines; references reviewed and updated.</td>
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<tr>
<td>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, liraglutide and lixisenatide respectively; updated dosage and administration for treatment naïve patients; references reviewed and updated.</td>
<td>03.12.19</td>
<td></td>
</tr>
<tr>
<td>RT4: updated FDA approved indications to reflect Victoza’s pediatric expansion to ages 10 and older.</td>
<td>06.25.19</td>
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### 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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.

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