Medication Policy Manual

**Policy No:** dru347

**Topic:** Non-Preferred Branded GLP1-Agonist-Containing Medications
- albiglutide (Tanzeum™)
- dulaglutide (Trulicity™)
- lixisenatide (Adlyxin™)
- lixisenatide/insulin glargine (Soliqua™)

**Date of Origin:** May 9, 2014

**Committee Approval Date:** July 14, 2017

**Next Review Date:** July 2018

**Effective Date:** August 1, 2017

**IMPORTANT REMINDER**

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

*Benefit determinations should be based in all cases on the applicable contract language.* To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

**Description**

Albiglutide (Tanzeum™), dulaglutide (Trulicity™), lixisenatide (Adlyxin™), and lixisenatide/insulin glargine (Soliqua™) are subcutaneously administered medications used for the treatment of type 2 diabetes. They resemble the human incretin hormone, glucagon-like-peptide 1 (GLP1).

*Note:* This policy does not apply to the liraglutide product marketed as Saxenda®.
Policy/Criteria

I. Most contracts require prior authorization approval of albiglutide, dulaglutide, and lixisenatide-containing medications prior to coverage. These medications may be considered medically necessary for the treatment of type 2 diabetes when criteria A, B, and C below are met.

A. Treatment with metformin is contraindicated, not tolerated, or has been ineffective after 90 days of therapy.

AND

B. Treatment with an exenatide-containing medication (e.g. Byetta, Bydureon) is contraindicated, not tolerated, or has been ineffective after 90 days of therapy

AND

C. Treatment with a liraglutide-containing product (e.g. Victoza, Xultophy) is contraindicated, not tolerated, or has been ineffective after 90 days of therapy

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx considers albiglutide, dulaglutide, liraglutide, and lixisenatide-containing medications to be self-administered medications.

B. When prior authorization is approved, non-preferred GLP-1 agonists may be approved in quantities as follows:

1. Albiglutide (Tanzeum): One package (four disposable, pre-filled, single-dose pens) per 28 days.

2. Dulaglutide (Trulicity): One package (four disposable, pre-filled, single-dose pens) per 28 days.

3. Lixisenatide (Adlyxin): One package (two disposable, pre-filled, multi-dose pens) per 28 days.

C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Albiglutide, dulaglutide, and lixisenatide-containing medications are considered investigational when used for any condition other than type 2 diabetes, including, but not limited to:

A. Pre-diabetes / Prevention of diabetes

B. Weight Loss

C. Islet-cell transplantation

D. Polycystic Ovary Syndrome

E. Type 1 diabetes or diabetic ketoacidosis

F. In combination with pramlintide (Symlin®) or exenatide (Byetta®, Bydureon®)
Position Statement

Summary
- Metformin (along with lifestyle changes) is the best value for the initial treatment of type 2 diabetes, with proven efficacy and safety track record.
- GLP1-agonists are treatment options when metformin results in inadequate glucose lowering or is not tolerated.
- Among the GLP1-agonists, exenatide-containing medications are the best value for members.
- The safety and effectiveness of GLP1-agonists in conditions other than type 2 diabetes have not been established.

Background
- The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have published a joint position statement on the management of type 2 diabetes. [1, 2]
  * Glycemic targets and glucose-lowering therapies must be individualized; however diet, exercise, and education remain the foundation of any type 2 diabetes treatment program.
  * The recommended therapy for newly diagnosed type 2 diabetes includes using metformin in addition to lifestyle interventions.
  * Metformin can lower A1C by about 1.8% compared to placebo and preliminary data suggest there are some potential cardiovascular benefits.
  * If a goal A1C of ≤ 7% is not achieved, then the addition of one or more oral or injectable agents from other classes is reasonable, depending on individual patient considerations.
  * Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.
  * Comprehensive cardiovascular risk reduction (e.g. controlling blood pressure, cholesterol, and smoking cessation) must be a major focus of therapy.

Goal of Treatment
- The American Diabetes Association has set an A1C treatment goal for patients with diabetes to not exceed 7%. [1]
  * Lowering A1C to below or around 7% has been shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes.
  * Large-scale, randomized controlled trials have failed to find a significant long-term benefit of intensive glycemic control (A1C goals less than 6.5%) for lowering cardiovascular (macrovascular) risk. [1, 3-5]
  * Intensive glycemic control (A1C goals less than 6.5%) may increase mortality in some patients. [3]
The American Association of Clinical Endocrinologists (AACE) treatment guidelines suggest an A1C treatment target for patients with diabetes of 6.5%. However, this goal must be customized for the individual patient in consideration of factors such as comorbid conditions, duration of diabetes, history of hypoglycemia, hypoglycemia unawareness, patient education, motivation, adherence, age, limited life expectancy, and use of other medications.\(^6\), \(^7\)

**Clinical Efficacy**

- GLP1-agonists lower A1C by up to 1% to 1.5%, but they have not been proven to reduce complications of diabetes.\(^{13-17}\)
- Metformin can lower A1C by up to 1.8% compared to placebo and is associated with reducing complications of diabetes.\(^8\)
- There are no clinical studies establishing conclusive evidence of macrovascular risk reduction with GLP1-agonists.\(^{13-17}\)
- There are no clinical trials that have demonstrated a superior benefit of GLP1-agonists over first line therapies such as metformin (see Appendix 1).
- There is no conclusive evidence that one GLP1-agonist is more effective than another in terms of cardiovascular risk. While the LEADER trial reported improved cardiovascular outcomes in patients with diabetes treated with liraglutide (Victoza) who were at high risk of cardiovascular events, trial results have not yet been published.\(^{29}\)
- In a head-to-head trial comparing liraglutide (Victoza) to exenatide ER (Bydureon), patients receiving liraglutide had a slightly lower average A1C (at end of study) than patients receiving exenatide ER (1.48 vs. 1.28, respectively [\(p<0.05\)]). This was accompanied by an increase in adverse event experiences by patients receiving liraglutide compared with exenatide ER, including substantially higher rates of nausea (20.4 vs. 9.3%), diarrhea (13.1 vs. 6.1%), and vomiting (10.7 vs. 3.7%).\(^{16}\)
- In a head-to-head trial comparing dulaglutide (Trulicity) to exenatide (Byetta), patients receiving dulaglutide had a slightly lower average A1C (at end of study) than patients receiving exenatide ER (1.5 vs. 1 respectively [\(p<0.001\)]). This was accompanied by an increase in adverse event experiences by patients receiving dulaglutide compared with exenatide, including higher rates of diarrhea (11 vs. 6%), and vomiting (17 vs. 11%).\(^{14}\)

**Safety**

- The most common adverse reactions include:
  - Albiglutide: (reported in \(\geq 10\)% of patients and more frequently than in patients on placebo) upper respiratory tract infection, diarrhea, nausea, and injection site reaction.\(^{13}\)
  - Dulaglutide: (reported in \(\geq 5\)% of patients and more frequently than in patients on placebo) nausea, diarrhea, vomiting, abdominal pain, and decreased appetite.\(^{14}\)
  - Liraglutide: (reported in \(\geq 5\)% of patients and more commonly than in patients treated with placebo) headache, nausea, diarrhea, and antibody formation.\(^{17}\)
The long-acting GLP-1 agonists have boxed warnings regarding the potential risk for medullary thyroid carcinoma. An increased incidence of thyroid C-cell tumors was observed in pre-clinical studies with GLP-1 agonists in animals. The relevance of this effect for humans is unknown. Risk of thyroid cancer is likely a class effect, which has been appreciated with more extensive post-marketing clinical experience. [13-17]

The prescribing information for GLP1-agonists lists a warning regarding the risk of acute pancreatitis. Risk of acute pancreatitis is small and likely a class effect, which has been appreciated with more extensive post-marketing clinical experience. The FDA is currently reviewing all incretin mimetics (DPP-4 inhibitors and GLP-1 agonists) for risk of pancreatitis and pancreatic cancer. [13-17, 24]

**Dosing**

- The recommended dose of albiglutide is 30 mg subcutaneously each week, which may be uptitrated to 50 mg weekly if required for adequate glycemic control. [13]
- The recommended dose of dulaglutide is 0.75 mg subcutaneously each week, which may be uptitrated to 1.5 mg weekly if required for adequate glycemic control. [14]
- The recommended dose of liraglutide is 1.2 to 1.8 mcg once daily. [17]
- The safety and effectiveness of higher doses have not been established.

**Investigational Conditions**

- Prediabetes / Prevention of Diabetes / Metabolic Syndrome
  * There are no clinical trials that have demonstrated that GLP1-agonists can prevent or delay the development of type 2 diabetes.
  * GLP1-agonists have not been proven to improve health outcomes in the treatment of “metabolic syndrome”.

- Weight Loss
  * Some medications used for the management of diabetes, such as DPP4-inhibitors and GLP1-agonists, have been associated with weight loss in clinical studies. It is unknown, however, if the observed weight reductions are clinically relevant and result in improved health outcomes.
  * There are currently no well-designed studies to establish the long-term maintenance or a progressive weight reduction with GLP1-agonists.
  * The FDA has approved a weight loss indication for liraglutide under the trade name Saxenda®. Overall, approximately 60% of patients lost 5% of their body weight, the FDA-defined endpoint. Adverse reactions included acute gallstone events, renal failure, cardiovascular effects, and gastrointestinal effects. Saxenda is dosed higher than Victoza (3mg daily). At this time, there is inadequate evidence for safety or efficacy to support the use of liraglutide (Victoza) for weight loss. [28]
- Polycystic Ovary Syndrome
  * There are no reliable clinical trials that have shown GLP1-agonists to be beneficial in the management of polycystic ovary disease.
  * Although not evaluated with liraglutide, a small, randomized, controlled trial evaluated the combination of exenatide (Byetta) with metformin in the management of women with polycystic ovary syndrome (PCOS). Though results suggested that the combination might have advantages over either agent alone, larger trials of longer duration are needed to assess long-term efficacy and safety. [23]

- Islet Cell Transplantation
  * Although not evaluated with liraglutide, small-scale trials have evaluated exenatide (Byetta) in the post-transplant management of patients who have received islet-cell transplantation for treatment of type 1 diabetes. This work is still preliminary, and remains investigational at this time. [26]

- Type 1 Diabetes / Diabetic Ketoacidosis
  * There are no well-designed, randomized controlled trials that demonstrate a benefit to using GLP1-agonists in type 1 diabetes.
  * The FDA approved prescribing information for the GLP1-agonists states that it should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. [13-17]
  * Although not evaluated with liraglutide, a small exploratory trial evaluated the effect of exenatide (Byetta) compared with insulin in eight children with type 1 diabetes. While suggestive of a positive effect on post-prandial glucose elevations, clearly larger, well designed clinical trials are necessary to establish the safety and efficacy of exenatide in this population.[27]

- In combination with pramlintide (Symlin) or exenatide (Byetta, Bydureon)
  * The safety and effectiveness of GLP-1 agonists have not been studied in combination with pramlintide (Symlin) or each other.
### Appendix 1: Comparison Of Product Information Reported Reductions In A1C (Monotherapy Only)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline A1C (%)</th>
<th>Duration of Trial</th>
<th>Mean change from baseline (%)</th>
<th>Placebo Corrected change in A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biguanide</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>metformin (Glucophage®, generic)</td>
<td>8.4</td>
<td>29 weeks</td>
<td>-1.4</td>
<td>-1.8</td>
</tr>
<tr>
<td>up to 2550 mg per day</td>
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<tr>
<td><strong>Dipeptidyl Peptidase-4 (DPP-4) Inhibitors</strong></td>
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<tr>
<td>alogliptin (Nesina®)</td>
<td>7.9</td>
<td>26 weeks</td>
<td>-0.6</td>
<td>-0.6</td>
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<tr>
<td>12.5 mg to 25 mg once daily</td>
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<td></td>
</tr>
<tr>
<td>linagliptin (Tradjenta®)</td>
<td>7.7 to 8.6</td>
<td>18 to 104 weeks</td>
<td>-0.4 to -0.7</td>
<td>-0.6 to -0.7</td>
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<tr>
<td>5 mg once daily</td>
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<tr>
<td>saxagliptin (Onglyza®)</td>
<td>7.9 to 8.0</td>
<td>24 weeks</td>
<td>-0.4 to -0.5</td>
<td>-0.6</td>
</tr>
<tr>
<td>2.5 mg to 5 mg once daily</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>sitagliptin (Januvia®)</td>
<td>8.0</td>
<td>18 to 24 weeks</td>
<td>-0.5 to -0.6</td>
<td>-0.6 to -0.8</td>
</tr>
<tr>
<td>100 mg once daily</td>
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<tr>
<td><strong>Glucagon-like Peptide-1 (GLP-1) Agonists</strong></td>
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<tr>
<td>albiglutide (Tanzeum®)</td>
<td>8.1</td>
<td>104 weeks</td>
<td>-0.6</td>
<td>-0.9</td>
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<tr>
<td>up to 50 mg weekly (with metformin)</td>
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<tr>
<td>dulaglutide (Trulicity™)</td>
<td>7.6</td>
<td>26 weeks</td>
<td>-0.9 to -1.1</td>
<td>-0.8 to -1.0</td>
</tr>
<tr>
<td>up to 1.5 mg weekly (with metformin)</td>
<td></td>
<td></td>
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<tr>
<td>exenatide (Byetta®)</td>
<td>8.2 to 8.3</td>
<td>30 weeks</td>
<td>-0.4 to -0.8</td>
<td>-0.5 to -0.9</td>
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<tr>
<td>up to 10 mcg twice daily (with metformin)</td>
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</tr>
<tr>
<td>exenatide ER (Bydureon®)</td>
<td>8.6</td>
<td>26 weeks</td>
<td>-1.5</td>
<td>N/A†</td>
</tr>
<tr>
<td>2 mg once weekly (with metformin)</td>
<td></td>
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<td></td>
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<tr>
<td>liraglutide (Victoza®)</td>
<td>8.3 to 8.4</td>
<td>26 weeks</td>
<td>-1.0</td>
<td>-1.1</td>
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<tr>
<td>up to 1.8 mg once daily (with metformin)</td>
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<td><strong>Meglitinide</strong></td>
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<tr>
<td>repaglinide (Prandin®)</td>
<td>8.5</td>
<td>12 weeks</td>
<td>-0.6</td>
<td>-1.7</td>
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<tr>
<td>up to 4 mg daily</td>
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<td><strong>Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors</strong></td>
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<tr>
<td>canagliflozin (Invokana®)</td>
<td>8.01</td>
<td>26 weeks</td>
<td>-1.03</td>
<td>-1.16</td>
</tr>
<tr>
<td>up to 300 mg once daily</td>
<td></td>
<td></td>
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<tr>
<td>dapagliflozin (Farxiga™)</td>
<td>8</td>
<td>24 weeks</td>
<td>-0.9</td>
<td>-0.7</td>
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<tr>
<td>up to 10 mg once daily</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>empagliflozin (Jardiance®)</td>
<td>7.9</td>
<td>24 weeks</td>
<td>-0.7</td>
<td>-0.7</td>
</tr>
<tr>
<td>up to 25 mg once daily</td>
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<td><strong>Sulfonylurea</strong></td>
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<tr>
<td>glimepiride (Amaryl®, generic)</td>
<td>unknown</td>
<td>14 weeks</td>
<td>unknown</td>
<td>-2.0</td>
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<tr>
<td>8 mg once daily</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Thiazolidinedione (TZD)</strong></td>
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<tr>
<td>pioglitazone (Actos®, generic)</td>
<td>10.2 to 10.3</td>
<td>26 weeks</td>
<td>-0.3 to -0.9</td>
<td>-1.0 to -1.6</td>
</tr>
<tr>
<td>30 mg to 45 mg daily</td>
<td></td>
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</table>

*Note: Data are pooled from separate studies or product literature and not necessarily comparable
† No placebo-controlled trials available
Cross References

Non-Preferred Branded DPP4-Inhibitor-Containing Medications, dru345
SGLT2-Inhibitor-Containing Medications, dru508

Codes | Number | Description
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N/A | | |

References


Revision History

<table>
<thead>
<tr>
<th>Revision Date</th>
<th>Revision Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>07/14/2017</td>
<td>Removed Victoza and Xultophy from policy (now preferred options).</td>
</tr>
<tr>
<td>03/06/2017</td>
<td>Added Xultophy to policy.</td>
</tr>
<tr>
<td>12/15/2016</td>
<td>Added Soliqua to policy.</td>
</tr>
<tr>
<td>08/12/2016</td>
<td>Added Adlyxin to policy with QL.</td>
</tr>
<tr>
<td>05/13/2016</td>
<td>No changes to coverage criteria with this annual update</td>
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</table>