Introduction

Metabolism refers to how the body converts the energy supplied by food into energy the body can use. Diabetes is a disease of the metabolic system. Diabetes involves production of and response to insulin. Insulin is a hormone produced by certain cells in the pancreas called beta cells. These cells regulate the amount of glucose (sugar) in the blood. There are two types of diabetes: type I and type II. In type I diabetes, the pancreas no longer makes insulin. The beta cells of the pancreas have been destroyed. The body needs an external supply of insulin in order to use glucose. Type I diabetes is usually diagnosed in children and young adults. In type II diabetes, people can still make insulin, but their bodies don’t respond well to it. This is known as insulin resistance. Type II diabetes can be diagnosed at any age and can be affected and modified by a number of factors, such diet and exercise and other health conditions. It can also be a side-effect of certain drugs. Type II diabetes can be treated with oral or injectable noninsulin agents, as well as insulin injections.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Documentation in the form of clinical chart notes is required for a review of all non-preferred agents.

<table>
<thead>
<tr>
<th>Metformin</th>
<th>GLP-1</th>
<th>GIP-GLP-1</th>
<th>Insulin +GLP-1</th>
<th>DPP-4</th>
<th>DPP-4 + Biguanide</th>
<th>SGLT-2</th>
<th>SGLT-2 + Biguanide</th>
<th>DPP-4 + SGLT-2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred</strong></td>
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<td>Bydureon</td>
<td>Mounjaro</td>
<td>Soliqua</td>
<td>Januvia</td>
<td>Janumet</td>
<td>Janumet XR</td>
<td>Jardiance</td>
<td>Synjardy</td>
<td>Glyxambi</td>
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<tr>
<td>Byetta</td>
<td></td>
<td>Xultophy</td>
<td>Tradjenta</td>
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<td>Jentadueto</td>
<td>Farxiga</td>
<td>Synjardy XR</td>
<td>Qtern</td>
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<td>Ozempic</td>
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<td>Jentadueto XR</td>
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<td>Xigduo XR</td>
<td>Trijardy XR</td>
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<td>Rybelsus</td>
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<td>Trulicity</td>
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<td>Victoza</td>
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<tr>
<td><strong>Non-Preferred</strong></td>
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<tr>
<td>Adlyxin</td>
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<td>Alogliptin / Metformin</td>
<td>Brenzavvy</td>
<td>Invokamet</td>
<td>Stegluican</td>
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<td></td>
<td>Kazano</td>
<td>Invokana</td>
<td>Invokamet XR</td>
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<td>Kombiglyze XR</td>
<td>Steglatro</td>
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<td>Segluromet</td>
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<td>Alogliptin / Pioglitazone</td>
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</tr>
</tbody>
</table>
Select the link below to view coverage criteria for non-preferred products:

- CD3-Directed Antibody (Intravenous)
- Insulin Products (Vials and Prefilled Pens)
- Insulin and Injectable Noninsulin Combination Products
- Injectable/Oral Noninsulin Products

**Note:** Documentation in the form of clinical chart notes is required for a review of all below-mentioned agents.

**CD3-Directed Antibody (Intravenous)**

<table>
<thead>
<tr>
<th><strong>Medical Benefit</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3-Directed Antibody (Intravenous)</td>
</tr>
<tr>
<td>• Tzield™ (teplizumab-mzwv)</td>
</tr>
</tbody>
</table>

**Coverage Criteria:** Tzield™ (teplizumab-mzwv) may be considered medically necessary to delay the onset of *Stage 3 type 1 diabetes (T1D)* in individuals with Stage 2 T1D when the following criteria are met:

- Individual is ≥ 8 years of age

**AND**

- Individual is at risk of developing T1D as documented by both of the following:
  - Presence of ≥ 2 autoantibodies
    - Glutamic acid decarboxylase 65 (GAD) autoantibody
    - Insulin autoantibody (IAA)
    - Insulinoma-associated antigen 2 autoantibody (IA-2A)
    - Zinc transporter 8 autoantibody (ZnT8A)
    - Islet cell autoantibody (ICA)
  - Evidence of dysglycemia on oral glucose tolerance testing
**Medical Benefit**

AND
- Tzield™ is administered as a once daily infusion for 14 consecutive days

AND
- Tzield™ is prescribed by or in consultation with an endocrinologist

**Note:** Stage 1 is defined by the appearance of autoantibodies, Stage 2 involves dysglycemia, and at Stage 3 there is autoimmune destruction of beta cells with elevated blood glucose and individual requires insulin treatment.

### Insulin Products (Vials and Prefilled Pens)

<table>
<thead>
<tr>
<th>Preferred Insulin</th>
<th>Non-preferred Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid–Acting Insulin</strong></td>
<td></td>
</tr>
<tr>
<td>• Novolog® (aspart)</td>
<td>• Humalog® (lispro)</td>
</tr>
<tr>
<td>• Fiasp® (aspart)</td>
<td>• Insulin lispro</td>
</tr>
<tr>
<td>• Insulin aspart</td>
<td>• Apidra® (glulisine)</td>
</tr>
<tr>
<td><strong>Coverage Criteria:</strong> No prior authorization required</td>
<td>• Admelog® (lispro)</td>
</tr>
<tr>
<td></td>
<td>• Admelog Solostar® (lispro)</td>
</tr>
<tr>
<td></td>
<td>• Lyumjev™ (lispro)</td>
</tr>
</tbody>
</table>

**Coverage Criteria:** For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type I or type II diabetes, and have a contraindication or intolerance to the preferred insulin OR this insulin product was ineffective in reducing A1C to goal after three months of therapy.

<p>| Regular-Acting/Short-acting Insulin |
|-----------------------------|-----------------------------|
| • Novolin R | • Humulin® R |
| <strong>Coverage Criteria:</strong> No prior authorization required | <strong>Coverage Criteria:</strong> For the above drug to be considered medically necessary, individual needs to have a diagnosis of type I or type II diabetes, and have a contraindication or intolerance to the preferred insulin OR this insulin product was |</p>
<table>
<thead>
<tr>
<th>Preferred Insulin</th>
<th>Non-preferred Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>ineffective in reducing A1C to goal after three months of therapy.</td>
<td></td>
</tr>
</tbody>
</table>

**Intermediate-Acting NPH Insulin**

- Novolin N

**Coverage Criteria:** No prior authorization required

- Humulin® N

**Coverage Criteria:** For the above drug to be considered *medically necessary*, individual needs to have a diagnosis of type I or type II diabetes, and have a contraindication or intolerance to the preferred insulin OR this insulin product was ineffective in reducing A1C to goal after three months of therapy.

**Mix of Intermediate-Acting NPH and Regular (Short-Acting) Insulin**

- Novolin Mix 70/30

**Coverage Criteria:** No prior authorization required

- Humulin® Mix 70/30

**Coverage Criteria:** For the above drug to be considered *medically necessary*, individual needs to have a diagnosis of type I or type II diabetes, and have a contraindication or intolerance to the preferred insulin OR this insulin product was ineffective in reducing A1C to goal after three months of therapy.

**Mix of Intermediate Insulin Lispro Protamine + Rapid-acting Insulin Lispro and Mix of Intermediate-acting Insulin Aspart Protamine + Rapid-acting Insulin Aspart**

- Novolog® Mix 70/30
- Insulin aspart protamine + insulin aspart mix 70/30

**Coverage Criteria:** No prior authorization required

- Humalog® Mix 75/25
- Humalog® Mix 50/50

**Coverage Criteria:** For the above drugs to be considered *medically necessary*, individual needs to have a diagnosis of type I or type II diabetes, and have a contraindication or intolerance to the preferred insulin OR this insulin product was ineffective in reducing A1C to goal after three months of therapy.

**Long–Acting Insulin**
Preferred Insulin

- Lantus® (glargine)
- Levemir® (detemir)
- Toujeo® (glargine)
- Tresiba® (degludec)

Coverage Criteria: No prior authorization required

Non-preferred Insulin

- Basaglar® (glargine)
- Insulin Degludec (degludec)
- Insulin Glargine (glargine-yfgn)
- Rezvoglar™ (glargine-aglr)
- Semglee™ (glargine-yfgn)

Coverage Criteria: For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type I or type II diabetes, and have a contraindication or intolerance to two preferred insulins OR these insulin products were ineffective in reducing A1C to goal after three months of therapy.

Insulin and Injectable Noninsulin Combination Products

Preferred Injectable

- Insulin and Glucagon-like Peptide-1 (GLP-1) Receptor Agonists
  - Soliqua® (insulin glargine+lixisenatide)
  - Xultophy® (insulin degludec+liraglutide)

Coverage Criteria: For the above drugs to be considered medically necessary, the individual needs to have a diagnosis of type II diabetes, and have an adequate trial of:
  - Metformin (unless contraindicated)

Injectable/Oral Noninsulin Products

Preferred

- Glucagon-like Peptide-1 (GLP-1) Receptor Agonists
  - Bydureon® and Bydureon BCise® (exenatide extended-release)
  - Byetta® (exenatide)
  - Ozempic® (semaglutide injectable)
  - Rybelsus® (semaglutide oral)
  - Trulicity® (dulaglutide)

Non-preferred

- Adlyxin® (lixisenatide)

Coverage Criteria: For the above drugs to be considered medically necessary, the individual
**Preferred**
- Victoza® (liraglutide)

**Coverage Criteria:** For the above drugs to be considered *medically necessary*, individual needs to have a diagnosis of type II diabetes, and have an adequate trial of:
- Metformin (unless contraindicated)

**Non-preferred**
needs to have a diagnosis of type II diabetes, and have an adequate trial of:
- Metformin (unless contraindicated)

**Coverage Criteria:**
- Two of the following:
  - Bydureon®/Bydureon BCise® (exenatide extended-release) or Byetta® (exenatide)
  - Mounjaro™ (tirzepatide)
  - Ozempic® (semaglutide injectable)
  - Rybelsus® (semaglutide oral)
  - Trulicity® (dulaglutide)
  - Victoza® (liraglutide)

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**Glucose-Dependent Insulinotropic Polypeptide (GIP) Receptor and Glucagon-like Peptide-1 (GLP-1) Receptor Agonists**

- Mounjaro™ (tirzepatide)

**Coverage Criteria:** For the above drug to be considered *medically necessary*, the individual needs to have a diagnosis of type II diabetes, and have an adequate trial of:
- Metformin (unless contraindicated)

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**Amylin Mimetics**

- Symlin® (pramlintide)

**Coverage Criteria:**
- To have a diagnosis of type I or type II diabetes

**Dipeptidyl Peptidase IV Inhibitors (DPP-4)**

- Januvia® (sitagliptin)
- Tradjenta® (linagliptin)
- Nesina (alogliptin)
- alogliptin
### Coverage Criteria:
For the above drugs to be considered **medically necessary**, individual needs to have a diagnosis of type II diabetes, and have an adequate trial of:

- Metformin (unless contraindicated)

### Non-preferred

- Onglyza® (saxagliptin)
- Oseni (alogliptin/pioglitazone)
- alogliptin/pioglitazone

### Coverage Criteria:
For the above drugs to be considered **medically necessary**, individual needs to have a diagnosis of type II diabetes, and have an adequate trial of:

- Metformin (unless contraindicated)

**AND**

- Two of the following:
  - Januvia® (sitagliptin)
  - Janumet® (sitagliptin + metformin)
  - Janumet® XR (sitagliptin + metformin extended release)
  - Jentadueto® (linagliptin + metformin)
  - Jentadueto® XR (linagliptin + metformin extended-release)
  - Tradjenta® (linagliptin)

### DPP-4 and Biguanide Combination

- Janumet® (sitagliptin + metformin)
- Janumet® XR (sitagliptin + metformin extended release)
- Jentadueto® (linagliptin + metformin)
- Jentadueto® XR (linagliptin + metformin extended-release)

### Coverage Criteria:
For the above drugs to be considered **medically necessary**, individual needs to have a diagnosis of type II diabetes, and have an adequate trial of:

- Metformin (unless contraindicated)

**AND**

- Two of the following:
  - Januvia® (sitagliptin)
  - Janumet® (sitagliptin + metformin)
  - Janumet® XR (sitagliptin + metformin extended release)
<table>
<thead>
<tr>
<th>Preferred</th>
<th>Non-preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jardiance® (empagliflozin)</td>
<td>Brenzavvy™ (bexagliflozin)</td>
</tr>
<tr>
<td>Farxiga® (dapagliflozin)</td>
<td>Invokana® (canagliflozin)</td>
</tr>
<tr>
<td>Tradjenta® (linagliptin)</td>
<td>Steglatro® (ertugliflozin)</td>
</tr>
</tbody>
</table>

**Sodium-Glucose Cotransporter 2 Inhibitors (SGLT-2)**
- Jentadueto® (linagliptin + metformin)
- Jentadueto® XR (linagliptin + metformin extended-release)
- Tradjenta® (linagliptin)

**Coverage Criteria:** For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type II diabetes, and have an adequate trial of:
- Metformin (unless contraindicated)

**Coverage Criteria:** For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type II diabetes, and have an adequate trial of:
- Metformin (unless contraindicated)
  - Two of the following:
    - Farxiga® (dapagliflozin)
    - Jardiance® (empagliflozin)
    - Synjardy® (empagliflozin + metformin)
    - Synjardy® XR (empagliflozin + metformin extended-release)
    - Xigduo® XR (dapagliflozin + metformin extended-release)

**SGLT-2 and Biguanide Combination**
- Synjardy® (empagliflozin + metformin)
- Synjardy® XR (empagliflozin + metformin extended-release)
- Xigduo® XR (dapagliflozin + metformin extended-release)

**Coverage Criteria:** For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type II diabetes, and have an adequate trial of:
- Metformin (unless contraindicated)

**Coverage Criteria:** For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type II diabetes, and have an adequate trial of:
- Metformin (unless contraindicated)
  - Two of the following:
<table>
<thead>
<tr>
<th>Preferred</th>
<th>Non-preferred</th>
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<tbody>
<tr>
<td>o Farxiga® (dapagliflozin)</td>
<td>o Jardiance® (empagliflozin)</td>
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<tr>
<td>o Jardiance® (empagliflozin)</td>
<td>o Synjardy® (empagliflozin + metformin)</td>
</tr>
<tr>
<td>o Synjardy® (empagliflozin + metformin)</td>
<td>o Synjardy® XR (empagliflozin + metformin extended-release)</td>
</tr>
<tr>
<td>o Xigduo® XR (dapagliflozin + metformin</td>
<td>o Xigduo® XR (dapagliflozin + metformin extended-release)</td>
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<td>extended-release)</td>
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</tbody>
</table>

DPP-4 and SGLT-2 Combination

- Glyxambi® (empagliflozin + linagliptin)
- Qtern® (dapagliflozin + saxagliptin)
- Trijardy™ XR (empagliflozin + linagliptin + metformin)

**Coverage Criteria:** For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type II diabetes, and have an adequate trial of:
- Metformin (unless contraindicated)

**Coverage Criteria:** For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type II diabetes, and have an adequate trial of:
- Metformin (unless contraindicated)

**AND**
- One of the following:
  o Glyxambi® (empagliflozin + linagliptin)
  o Qtern® (dapagliflozin + saxagliptin)
  o Trijardy™ XR (empagliflozin + linagliptin + metformin)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>As listed</td>
<td><strong>Future re-authorization of Tzield™ (teplizumab-mzwv) beyond the once daily infusion for 14 consecutive days is considered investigational.</strong></td>
</tr>
</tbody>
</table>

All other uses of the drugs for conditions not listed in this policy, for quantities that exceed the FDA labeled dosing, or for a condition not outlined in Policy 5.01.605 are considered investigational.

- Use of Victoza® (liraglutide) for weight management is considered investigational. Please see Saxenda® (liraglutide) criteria in Policy 5.01.621 Drugs for Weight Management.
### Drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Use of Ozempic® (semaglutide) for weight management is considered investigational. Please see Wegovy™ (semaglutide) criteria in Policy 5.01.621 Drugs for Weight Management.</td>
</tr>
</tbody>
</table>

### Drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Not Medically Necessary</th>
</tr>
</thead>
<tbody>
<tr>
<td>As listed</td>
<td>All other uses of the drugs for approved conditions listed in this policy or for approved conditions listed in Policy 5.01.605 are considered not medically necessary.</td>
</tr>
</tbody>
</table>

### Length of Approval

<table>
<thead>
<tr>
<th>Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial authorization</td>
<td>Tzield™ (teplizumab-mzwv) will be approved for a once daily infusion for 14 consecutive days. All other drugs listed in policy may be approved up to 3 years.</td>
</tr>
<tr>
<td>Re-authorization criteria</td>
<td>Future re-authorization of Tzield™ (teplizumab-mzwv) beyond the once daily infusion for 14 consecutive days is considered investigational. Future re-authorization of all other drugs listed in policy may be approved up to 3 years as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.</td>
</tr>
</tbody>
</table>

### Documentation Requirements

The individual’s medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:
- Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

### Coding
### Benefit Application

**Tzield™** (teplizumab-mzwv) is managed through the medical benefit. All other drugs addressed in this policy are managed through the Pharmacy benefit.

### Evidence Review

### Insulin Agents

**Table 1. Types and Characteristics of Commonly Used Insulin Products**

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Brand Name</th>
<th>Onset of Action</th>
<th>Peak Effect</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting Insulin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro</td>
<td>Humalog</td>
<td>&lt; 15 minutes</td>
<td>30 to 90 minutes</td>
<td>3 to 5 hours</td>
</tr>
<tr>
<td>Aspart</td>
<td>Novolog</td>
<td>&lt; 15 minutes</td>
<td>30 to 90 minutes</td>
<td>3 to 5 hours</td>
</tr>
<tr>
<td>Glulisine</td>
<td>Apidra</td>
<td>&lt; 15 minutes</td>
<td>30 to 90 minutes</td>
<td>3 to 5 hours</td>
</tr>
<tr>
<td><strong>Short-acting Insulin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>Humulin R</td>
<td>0.5 to 1 hour</td>
<td>2 to 4 hours</td>
<td>4 to 8 hours</td>
</tr>
<tr>
<td>Insulin</td>
<td>Brand Name</td>
<td>Onset of Action</td>
<td>Peak Effect</td>
<td>Duration of Action</td>
</tr>
<tr>
<td>---------------------------</td>
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<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Novolin R</td>
<td></td>
<td>0.5 to 1 hour</td>
<td>2 to 4 hours</td>
<td>4 to 8 hours</td>
</tr>
</tbody>
</table>

**Intermediate-acting Insulin**

| NPH                       |                           | 1 to 2 hours    | 4 to 10 hours| 10 to 18 hours     |

**Long-acting Insulins**

| Degludec                  | Tresiba                    | 0.5 to 1.5 hours| No peak     | 42 to 45 hours     |
| Detemir                   | Levernir                   | 1 to 2 hours   | 3 to 9 hours| 6 to 24 hours *    |
| Gliargine                 | Basaglar                   | 1 to 2 hours   | No peak     | 20 to 24 hours     |
| Gliargine                 | Lantus                     | 1 to 2 hours   | No peak     | 20 to 24 hours     |
| Gliargine                 | Semglee                    | 1 to 2 hours   | No peak     | 20 to 24 hours     |
| Gliargine                 | Toujeo                     | 6 hours        | No peak     | Up to 36 hours     |

**Combination Insulins**

| Mix of intermediate insulin lispro protamine and rapid-acting insulin lispro and | Humulin 70/30 and Novolin 70/30 | 0.5 to 1 hour | 2 to 10 hours | 10 to 18 hours |
| Mix of intermediate-acting insulin aspart protamine and rapid-acting insulin aspart | Humalog 75/25 and Novolog 70/30 | <15 minutes  | 1 to 2 hours  | 10 to 19 hours |

*Duration of action for detemir is dose-dependent.

**Insulin Interchangeability**

As shown in the table above, different brand name insulin products can have similar pharmacokinetic profiles. Currently, there is no scientific literature or evidence to suggest that one insulin brand is superior over the other. Switching between insulin brands should be done in consultation with a physician and requires medical supervision (close monitoring of blood glucose) during the initial phase.
Injectable Noninsulin Agents

Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

GLP-1 agonists are indicated as an adjunct to diet and exercise for glycemic control in adults with T2DM. Adlyxin, Bydureon, Byetta, Ozempic, Trulicity, and Victoza are available as SQ injections with Rybelsus being available as an oral tablet. Byetta is administered twice daily, Adlyxin, Rybelsus and Victoza are once daily, and all others administered once weekly. GLP-1 agonists act to enhance glucose-dependent insulin secretion, suppress glucagon secretion, and slow gastric emptying. GLP-1 agonists also decrease body weight and systolic blood pressure. GLP-1 agonists are currently recommended as dual or triple therapy with metformin by the ADA.

Most significantly, a large, well-designed head-to-head trial with liraglutide and exenatide ER found liraglutide significantly more effective in decreasing HbA1c. Additional data indicates exenatide twice daily (Byetta) is associated with less reduction in HbA1c than other GLP-1 agonists. Efficacy and safety data are now available to 5 years with exenatide ER. Common AE include nausea, vomiting, and diarrhea as well as injection site reactions with exenatide ER and albiglutide. The class carries a black box warning for use in individuals with a history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. While cardiovascular outcomes studies are on-going, available data with short-term trials does not indicate increased risk. Cost-effectiveness analyses have found GLP-1 agonists cost effective in comparison to other brand agents for T2DM and liraglutide cost effective in comparison to exenatide ER. Cost effectiveness comparisons with generic agents are not available.

A newer agent in this class is called lixisenatide is a GLP-1 receptor agonist that has been shown to have significant effect on reducing HbA1c %, 2-h PPG, and modest weight loss benefit from 9 DB placebo-controlled RCTs and 5 meta-analysis. From the perspective of safety, it is considered generally well tolerated. The most common side effect is GI disorders (N/V/D), and the occurrence is more frequent than insulin and OADs. Of note, it has significantly less hypoglycemia than insulin. Based on the results from four phase 3 or phase 4 active-controlled RCTs, compared to other GLP-1 receptor agonists in the same drug class, lixisenatide does not appear to be relatively more efficacious or safer. Currently, there is no cost-effectiveness analysis conducted in a US setting.
Glucose-Dependent Insulinotropic Polypeptide (GIP) Receptor and Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

Tirzepatide is a dual GIP and GLP-1 receptor agonist. It is a 39-amino acid synthetic peptide based on the GIP sequence and is modified with a C20 fatty diacid moiety that binds to albumin and increases the half-life. Tirzepatide enhances first- and second-phase insulin secretion, and reduces glucagon levels, both in a glucose-dependent manner. Tirzepatide is injected subcutaneously once weekly and is FDA-approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

A phase 3 head-to-head open-label trial (SURPASS-2) explored the efficacy and safety of tirzepatide compared to injectable semaglutide. Individuals were randomized 1:1:1:1 to tirzepatide 5 mg (n= 470), 10 mg (n= 469), 15 mg (n= 470) or semaglutide 1mg (n= 469) every week for 40 weeks followed by a 4-week safety period. 1,878 individuals included in the study were adults with T2DM that were inadequately controlled with metformin at a dose of at least 1500 mg per day. Included individuals also had HbA1c levels of 7.0 to 10.5% and a BMI of ≥ 25 kg/m2 with a stable weight in the past three months. Individuals with type 1 diabetes, an eGFR below 45 mL/min/1.73 m2, and a history of pancreatitis were excluded from the study. Included individuals had a mean age of 56.6 years, with 53% identifying as female, 82.6% white, an average weight of 93.7 kg, and an eGFR of 96.0 mL/min/1.73 m2. The primary endpoint was change in HbA1c from baseline to week 40. Secondary endpoints include change from body weight, and attainment of HbA1c targets of less than 7.0% and less than 5.7%. From a baseline HbA1c of 8.28%, tirzepatide 5, 10, and 15 mg decreased HbA1c to 6.19, 5.91 and 5.82% respectively at 40 weeks compared to 6.42% in the semaglutide group. The estimated treatment difference (ETD) of tirzepatide vs semaglutide was statistically significant (ETD -0.15 p=0.02, -0.39 p<0.001, -0.45 p<0.001 for 5, 10, 15 mg respectively vs semaglutide). Body weight reductions were dose dependent and significant compared to semaglutide (ETD -1.9, -3.6, -5.5 kg respectively, p<0.001 for all comparisons). Proportion of participants who met glycated hemoglobin requirements of <7.0% were similar across all groups with 79% of the semaglutide group, 82% of the tirzepatide 5mg group and 86% of both tirzepatide 10mg, 15mg (p<0.05 for tirzepatide 10, 15mg vs semaglutide).

Amylin Mimetics (pramlintide)

Pramlintide is an amylin analog designed for individuals with type 1 or type 2 diabetes who use mealtime insulin and have failed to achieve desired glycemic control despite optimal insulin therapy. Amylin is a 37-amino acid peptide that is stored in pancreatic beta cells and is co-
secreted with insulin and has a similar plasma kinetic profile. It affects glucose control through several mechanisms, including slowed gastric emptying, regulation of postprandial glucagon, and reduction of food intake. Glucose influx is better regulated, allowing exogenous insulin therapy to more easily match physiologic needs. Pramlintide is dosed before major meals and titrated as tolerated. Pramlintide has an anorexic effect and carries a black box warning for risk of severe hypoglycemia. This risk may be reduced by careful individual selection and instruction, and by insulin dose reduction.

Pramlintide has been studied in randomized controlled trials in both type 1 and type 2 diabetes. In type 1 diabetes, 30 to 60 mcg of pramlintide administered subcutaneously with meals resulted in sustained, albeit modest (<1 percentage point) reductions in glycated HbA1c over the 52-week trial. More than twice as many individuals (25 versus 11.3 percent) achieved an A1c of less than 7% in the treatment group vs. placebo, with no increase in insulin dose or incidence of severe hypoglycemia. Modest reductions in body weight (mean of 0.5 kg) were seen in the treatment group, compared with weight gain in individuals receiving insulin only.

In a 24-week trial of individuals with inadequately controlled type 2 diabetes, the addition of preprandial pramlintide to basal insulin with or without oral agents had similar glycemic efficacy as the addition of premeal rapid acting insulin analogs (A1c reduction of approximately 1%). Individuals randomly assigned to pramlintide maintained their weight, whereas those assigned to rapid acting insulin gained weight (mean 4.7 kg). Pramlintide was associated with fewer hypoglycemic events compared with prandial insulin. In addition to modest reductions in A1c and weight, pramlintide has been associated with reductions in postprandial glucose excursions and in surrogate markers of cardiovascular risk and oxidative stress. The clinical implications of these findings are unknown.

A recent meta-analysis included ten RCTs that evaluated the use to pramlintide as adjunct treatment with insulin in individuals with type I diabetes. Pramlintide was found to reduce HbA1c by a mean of 0.41%, reduce TDD of insulin, and reduce body weight. With regard to safety, pramlintide had significantly more reported incidence of hypoglycemia, nausea, vomiting, and anorexia.
Insulin and Injectable Noninsulin Combination Products

Insulin and Glucagon-Like Peptide-1 Receptor Agonists

Xultophy® (insulin degludec and liraglutide)

Xultophy® (insulin degludec/liraglutide) combines two complementary mechanisms of action into a once daily self-injection. Six trials have been published, all of which have shown equal or improved efficacy to active comparators in individuals above HbA1c goal. IDegLira has received a narrow indication for individuals inadequately controlled on liraglutide (less than 1.8 mg daily) or basal insulin (less than 50 units daily). This individual population can better reach goal using the combination product without negatively affecting adherence rates. The combination product offers benefits in terms of efficacy, safety and cost compared to alternative strategies such as basal-bolus dosing, using the separate products in multiple doses, and up-titrating a basal insulin. While the trials largely excluded those with a BMI above 40 kg/m², the consistent positive results in disparate treatment groups suggests strong Phase III evidence for insulin degludec/liraglutide.

Soliqua® (insulin glargine and lixisenatide)

Soliqua® (insulin glargine and lixisenatide) like Xultophy® combines two complementary mechanisms of action into a once daily self-injection. iGlarLixi was studied in two clinical trials: 1. LixiLan-L: in individuals uncontrolled on basal insulin, with or without previous exposure to metformin, with insulin glargine alone as comparator; and 2. LixiLan-O: in individuals uncontrolled on 2 or more oral anti-diabetic drugs, with insulin glargine alone, and lixisenatide alone as comparators. In study 1, Soliqua showed superiority to insulin glargine alone in terms of hemoglobin A1C reduction, with no increase in hypoglycemia or weight. Fasting plasma glucose (FPG) reduction with Soliqua was comparable to that of insulin glargine alone. Post prandial glucose (PPG) reduction with Soliqua was greater than that of insulin glargine alone. In study 2, Soliqua showed superiority to insulin glargine alone and lixisenatide alone with regard to hemoglobin A1C reduction with no increases in hypoglycemia (as compared to glargine). FPG reduction with Soliqua was comparable to that of insulin alone and great than that of lixisenatide alone. Redution in 2-h PPG with Soliqua was greater than that of insulin glargine alone and lixisenatide alone. Study also showed that Soliqua resulted in significantly greater weight loss compared with insulin glargine alone, but demonstrated less weight loss compared with lixisenatide alone. For full description of the clinical trials, please refer to the package insert.
Oral Agents

Dipeptidyl Peptidase IV Inhibitors (DPP-4 inhibitors)

Comparisons with DPP-4 inhibitors and placebo have found the class decreases HbA1c approximately -0.56% to -0.8%. Trials assessing these agents as add-on therapy have found similar HbA1c decreases. No difference in efficacy has been found between DPP-4 inhibitors and other add-on therapy for diabetes including sulfonylureas and TZDs; however, DPP-4 inhibitors are less effective than metformin. Head-to-head trials with saxagliptin and sitagliptin have found no difference between agents; however, no comparative data is available to date with newer agents (linagliptin and alogliptin). Long-term trial data is available for all agents. The ADA guidelines recommend the class as an option along with sulfonylureas, TZDs, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin for add-on therapy with metformin.

The agents are generally well tolerated with little hypoglycemia unless given with insulin or sulfonylureas. The DPP-4 inhibitors appear weight neutral. Reports of pancreatitis have led to an FDA warning; however, trial data does not consistently support this and further study is needed. Several recent randomized controlled trials have indicated that DPP-4 inhibitors did not increase the risk of adverse cardiovascular outcomes. However, the SAVOR-TIMI 53 study found an increase rate of heart failure hospitalization. Further study is ongoing.

Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors

SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) are oral agents indicated to improve glycemic control in adults with T2DM as an adjunct to diet and exercise. A couple of SGLT2 drugs, Farxiga® (dapagliflozin) and Jardiance® (empagliflozin), are also approved for non-diabetes specific indications. Jardiance is approved for the treatment of individuals with a diagnosis of chronic heart failure while Farxiga is approved for the treatment of individuals with a diagnosis of chronic heart failure and for the treatment of chronic kidney disease. SGLT2 inhibitors decrease glucose reabsorption in the proximal nephron and increase urinary glucose excretion. The mechanism of action of SGLT2 inhibitors is not dependent on insulin.

Large, well-designed, long-term trials and meta-analyses have shown SGLT2 inhibitors decrease HbA1c in comparison to placebo (-0.7 to -1.1%). SGLT2 inhibitors have been extensively studied in dual and triple therapy regimens, typically as add-on agents to metformin, SUs, DPP4s, and TZDs. Since the last review, new data has become available supporting the use of dapagliflozin in triple therapy regimens. Additionally, longer duration trials to 104 weeks have been published indicating continued effectiveness. Trials comparing SGLT2 inhibitors to other classes of agents...
have found no difference in effectiveness in comparison with metformin. However, available data conflicts about the efficacy of SGLT2 inhibitors in comparison to other classes (SU, TZDs, and DPP4s) with some data indicating superiority and others non-inferiority. In addition, trials with SGLT2 inhibitors are associated with decreased body weight and BP. Adverse events with SGLT2 inhibitors include genital mycotic infections, UTIs, and, less commonly, volume depletion and renal-related effects. The FDA has recently issued two safety warnings for the class, concerning an increased risk of DKA across the class as well as increased incidence of upper extremity, low-trauma fractures with canagliflozin. Further research is needed to fully define these effects as well as the CV effects of the class. Cost effectiveness studies in the US setting comparing SGLT2 inhibitors to other classes of agents for T2DM are not available and drug costs remain high.

**EMPA-REG: CV Outcomes Trial Summary**

The goal of the trial was to examine the long-term effects of empagliflozin versus placebo, in addition to standard of care (such as, lifestyle, risk reduction with antihypertensive treatment, statins, aspirin, and metformin), on cardiovascular (CV) morbidity and mortality in individuals with T2DM and high risk of CV events. This was a randomized (1:1:1 to empagliflozin 10mg, 25mg, and placebo), double-blind, placebo-controlled, international CV outcomes trial. Total number of participants was 7,028. This was an industry-sponsored trial.

Key findings included:

- The primary outcome, CV death, nonfatal MI, or stroke for empagliflozin vs. placebo: 10.5% vs. 12.1%, hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.74 to 0.99, \( p<0.001 \) for non-inferiority; \( p=0.04 \) for superiority.
  - For CV death: 3.7% vs. 5.9%, \( p<0.001 \)
  - All MI: 4.8% vs. 5.4%, \( p=0.23 \)
  - All stroke: 3.5% vs. 3.0, \( p=0.26 \)
- Reduced risk of composite cardiovascular events (NNT=63/3 years) and all cause death (NNT=38/3 years). The 10mg daily dose provided almost the same benefit as the 25mg dose. Benefit realized despite A1C not reaching target (A1C=7.8%). Mean change was about \( \leq 0.6\% \).
• Increased risk of genital infections in both males (NNH=29/3 years) and females (NNH=14/3 years). Urosepsis, although rare, was also increased with empagliflozin (~0.4% vs. 0.1%). Serious Adverse Events (SAE) were less with empagliflozin than placebo (NNT=24). A

• Empagliflozin also lowered systolic blood pressure (SBP) by 3 to 4 mm Hg, and diastolic blood pressure (DBP) by 1 to 2 mm Hg.

• Weight was also noted to decrease by about 1 to 2 kg, which was more than in the placebo group.

• Average A1C achieved in the empagliflozin group was 7.8%.

For details on secondary outcomes (all-cause mortality, congestive heart failure (CHF) hospitalization, CV death, all cause hospitalization, coronary revascularization, A1C at 12 weeks for 10mg dose, A1C at 12 weeks for 25mg dose, confirmed hypoglycemic event, and urinary tract infection rates), and for renal outcomes (incident or worsening nephropathy, doubling of serum creatinine, progression to macroalbuminuria, and initiation of renal replacement therapy), please refer to the American College of Cardiology article, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Individuals- EMPA-REG Outcome. Available at: https://www.acc.org/latest-in-cardiology/clinical-trials/2015/09/17/10/11/empa-reg-outcome. (Accessed April 10, 2023).

The results of this trial demonstrate that empagliflozin is superior to placebo in improving glycemic control and reducing CV events in individuals with type 2 diabetes and established cardiovascular disease. The fact that CV safety is thought to be established in this trial is an important factor in light of the prior serious safety concerns involving rosiglitazone. However, the mechanism for this benefit is still unknown (and may be due to non-glucose related mechanism).

Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results (LEADER) Trial

The goal of this trial was to examine the long-term effects of liraglutide on cardiovascular outcomes and other clinically important events. This was a multicenter, double-blind, randomized (1:1), placebo-controlled trial at 410 sites in 32 countries, and included a total of 9,340 participants. Trial follow-up was about 3.8 years (+/- 3 months). Selected individuals had established cardiovascular disease, chronic kidney disease of stage 3 or greater, or both (in addition to having diabetes). This trial was supported by Novo Nordisk and by grants from the National Institutes of Health.
Key findings for the primary outcomes included:

- The primary composite outcome (the first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke) occurred fewer in individuals in the liraglutide group, 608 of 4668 (13.0%) than in the placebo group, 694 of 4672 (14.9%); HR 0.87 with 95% CI; 0.78 to 0.97, p<0.001 for non-inferiority; p=0.01 for superiority.

- Death from CV causes occurred in fewer individuals in liraglutide group, 219 individuals (4.7%) than in the placebo group, 278 (6.0%); HR 0.78; with 95% CI, 0.66 to 0.93; p=0.007.

- Rate of death from any cause was lower in liraglutide group, 981 individuals (8.2%) than in the placebo group, 447 (9.6%); HR 0.85; 95 CI, 0.74 to 0.97; p=0.02.

- Nonfatal MIs were fewer in the liraglutide group than in the placebo group, but not significant

- Nonfatal stroke events were fewer in the liraglutide group than in the placebo group, but not significant

- Glycemic control analysis showed a mean difference in A1C between the liraglutide group and placebo of -0.40 percentage points (95% CI, -0.45 to -0.34)

- Weight loss was 2.3 kg (95%CI, 2.5 to 2.0) higher in the liraglutide group

- Systolic blood pressure was 1.2 mm Hg (95% CI, 1.9 to 0.5) lower in the liraglutide group, however, the diastolic blood pressure was 0.6 mm Hg (95% CI, 0.2 to 1.0) higher in liraglutide group (and so was the heart rate at 3.0 beats per minute 95%CI, 2.5 to 3.4)


The results of this trial suggest that liraglutide has lower rates of CV events and death form any cause when compared to placebo, however, this study has a few limitations, such as relatively short period of follow-up, and the fact that participants in the study already had high risk for CV events, and had a mean baseline A1C of 8.7%, which makes it challenging to apply these findings to individuals with milder forms of the disease. It is important to recognize that the findings of CV benefits in this trial are different from the ones described in EMPA-REG trial, particularly the time to benefit was seen earlier in EMPA-REG than in the current study.
Practice Guidelines and Position Statements

Table 1. American Association of Clinical Endocrinologists and American College of Endocrinologists (AACE/ACE) Comprehensive Diabetes Management Algorithm (2019)

<table>
<thead>
<tr>
<th>Goals for Glycemic Control of Type 1 and Type 2 Diabetes Mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
</tr>
<tr>
<td>Goals are tailored to each person’s individual needs on the basis of age, comorbidities (cardiovascular disease, hyperlipidemia, renal disease, etc.), duration and extent of diabetes*</td>
</tr>
<tr>
<td>For individuals without concurrent illness and at low hypoglycemic risk: ≤ 6.5%</td>
</tr>
<tr>
<td>For individual with concurrent illness and at risk for hypoglycemia: &gt;6.5%</td>
</tr>
<tr>
<td>Pre-Prandial Plasma Glucose</td>
</tr>
<tr>
<td>Peak Post-Prandial Glucose</td>
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</tbody>
</table>

*Considerations should include residual life expectancy; duration of diabetes; presence or absence of microvascular (renal and retinal) and macrovascular (CV) complications; CVD risk factors; comorbid conditions; risk for severe hypoglycemia (especially in older adults); and psychological, social, and economic status (affordability of treatment choice can have impact on compliance). Adapted from AACE Diabetes Resource Center.

Type 1 and Type 2 Diabetes Mellitus Management

Current and complete list of recommendations from AACE/ACE can be found at:

- For Type 1: [https://pro.aace.com/disease-state-resources/diabetes/depth-information/treatment-type-1-diabetes](https://pro.aace.com/disease-state-resources/diabetes/depth-information/treatment-type-1-diabetes)

U.S. Preventive Services Task Force Recommendations

Published recommendations include:
- Screening for type 2 diabetes in asymptomatic adults with sustained blood pressure (either treated or untreated) greater than 135/80 mm Hg.

- Gestational Diabetes Mellitus Screening for asymptomatic pregnant women after 24 weeks of gestation.

References


**History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/31/16</td>
<td>New Policy, add to Prescription Drug section. Policy effective date is October 1, 2016.</td>
</tr>
<tr>
<td>12/01/16</td>
<td>Interim Review, approved November 8, 2016. New GLP-1 agent, called Adlyxin® (lixisenatide) was added to the non-preferred GLP-1 agonist criteria.</td>
</tr>
<tr>
<td>02/10/17</td>
<td>Annual Review, approved January 10, 2017. Added new agents Xultophy and Soliqua to the policy. Updated corresponding description and references sections.</td>
</tr>
<tr>
<td>04/01/17</td>
<td>Interim Review, approved March 14, 2017. Updated formulary status for Xultophy and Soliqua, previously non-preferred.</td>
</tr>
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<td>Date</td>
<td>Comments</td>
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<tr>
<td>10/01/17</td>
<td>Interim Review, approved September 12, 2017. Added Symlin (pramlintide) and updated description and reference sections.</td>
</tr>
<tr>
<td>11/01/17</td>
<td>Interim Review, approved October 19, 2017. Updated criteria if metformin is contraindicated.</td>
</tr>
<tr>
<td>11/07/17</td>
<td>Minor formatting updates.</td>
</tr>
<tr>
<td>01/01/18</td>
<td>Interim Review, approved December 20, 2017. Added Ozempic as a preferred injectable noninsulin product.</td>
</tr>
<tr>
<td>03/01/18</td>
<td>Annual Review, approved February 6, 2018. Policy updated with literature review through January 2018. Steglatro added as a preferred SGLT-2 product. Admelog® (lispro) and Admelog Solostar® (lispro) added as non-preferred rapid acting insulin products. Reference 25 added. No changes to policy statement.</td>
</tr>
<tr>
<td>04/01/18</td>
<td>Interim Review, approved March 13, 2018. Soliqua moved to nonpreferred status under insulin and Glucagon-like Peptide-1 (GLP-1) Receptor Agonists, Qtern and Steglujan were added as preferred Dipeptidyl Peptidase IV Inhibitor (DPP-4) and Sodium–Glucose Cotransporter 2 Inhibitor.</td>
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<tr>
<td>04/01/19</td>
<td>Annual Review, approved March 19, 2019. Policy updated with literature review through February 2019. Updated glycemic control recommendations from AACE/ACE 2019 guidelines. No evidence was found that would change the criteria in this policy.</td>
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<tr>
<td>08/01/19</td>
<td>Interim Review, approved July 25, 2019. Added Basaglar® (insulin glargine), Fiasp® (insulin aspart), insulin lispro and Bydureon BCise® (exenatide extended-release) to policy.</td>
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<tr>
<td>11/01/19</td>
<td>Interim Review, approved October 8, 2019. Added Trulicity as a preferred GLP-1 receptor agonist and moved Victoza to non-preferred. Added coverage criteria for Rybelsus and updated coverage criteria for Adlyxin, Tanzeum and Victoza which are the non-preferred GLP-1 receptor agonists.</td>
</tr>
<tr>
<td>01/01/20</td>
<td>Interim Review, approved December 17, 2019. Added Rybelsus as a preferred GLP-1 receptor agonist.</td>
</tr>
<tr>
<td>02/01/20</td>
<td>Interim Review, approved January 23, 2020. Added authorized generic for insulin aspart and insulin aspart protamine mix 70/3 as preferred.</td>
</tr>
<tr>
<td>08/01/20</td>
<td>Interim Review, approved July 14, 2020. Added coverage criteria to the long-acting insulin Basaglar (glargine). For DPP-4 medications moved Onglyza (saxagliptin) to non-preferred and Tradjenta (linagliptin) to preferred. Updated coverage criteria for all non-preferred DPP-4 medications. For DPP-4 and Biguanide Combination medications moved Kombiglyze XR (saxagliptin + metformin extended release) to non-preferred and Jentadueto (linagliptin + metformin) and Jentadueto XR (linagliptin + metformin extended-release) to preferred. Updated coverage criteria for all non-preferred DPP-4 and Biguanide Combination medications. For SGLT-2 medications moved Invokana (canagliflozin) and Steglatro (ertugliflozin) to non-preferred. Updated coverage criteria for all non-preferred SGLT-2 medications. Added a new section for SGLT-2 and Biguanide Combination medications and added coverage criteria for Invokamet.</td>
</tr>
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<td>Date</td>
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<tr>
<td>09/01/20</td>
<td>Annual Review, approved August 20, 2020. Added Rybelsus (semaglutide oral) as one of the qualifying drugs for the non-preferred GLP-1 receptor agonists Adlyxin, Tanzeum, and Victoza. For Victoza added an exception for patients less than 18 years of age regarding use of two preferred GLP-1 receptor agonists.</td>
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<tr>
<td>12/01/20</td>
<td>Interim Review, approved November 10, 2020. Added Semglee (glargine) to policy as a non-preferred long-acting insulin. For DPP-4 and SGLT-2 Combination medications moved Glyxambi (empagliflozin + linagliptin) and Trijardy XR (empagliflozin + linagliptin + metformin) to preferred and updated the non-preferred criteria for Steglujan (ertugliflozin + sitagliptin) to require an adequate trial with either Glyxambi, Qtern (dapagliflozin + saxagliptin), or Trijardy XR.</td>
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<tr>
<td>03/01/21</td>
<td>Annual Review, approved February 18, 2021. Changed Soliqua (insulin glargine+lixisenatide) to a preferred insulin and GLP-1 receptor agonist product. Removed reference to Tanzeum (albiglutide) from policy as the drug was discontinued by manufacturer.</td>
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<tr>
<td>09/01/21</td>
<td>Interim Review, approved August 24, 2021. Added a table for when drugs listed are considered investigational or not medically necessary, added a length of approval table, and added a documentation requirements table.</td>
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<tr>
<td>05/01/22</td>
<td>Annual Review, approved April 25, 2022. Added brand Insulin Glargine (glargine-yfgn) as a non-preferred long-acting insulin.</td>
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<tr>
<td>07/01/22</td>
<td>Interim Review, approved June 27, 2022. Added coverage criteria for Mounjaro (tirzepatide), a dual GIP and GLP-1 receptor agonist, for the treatment of type 2 diabetes.</td>
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<tr>
<td>10/01/22</td>
<td>Interim Review, approved September 13, 2022. Changed Mounjaro to preferred GIP/GLP-1 receptor agonist. Added Mounjaro as one of the qualifying drugs for the non-preferred GLP-1 receptor agonists Adlyxin and Victoza. Changed policy wording from &quot;patient&quot; to &quot;individual&quot; for standardization.</td>
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<tr>
<td>11/01/22</td>
<td>Interim Review, approved October 11, 2022. Changed Victoza to preferred GLP-1 receptor agonist. Added Victoza as one of the qualifying drugs for the non-preferred GLP-1 receptor agonists Adlyxin.</td>
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<tr>
<td>03/01/23</td>
<td>Interim Review, approved February 14, 2023. Added coverage for Tzield (teplizumab-mzwv) to delay the onset of Stage 3 T1D in individuals with Stage 2 T1D. Added</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
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<td>------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td>04/01/23</td>
<td>Brenzavvy (bexagliflozin) to policy as a non-preferred SGLT2 inhibitor. Added HCPC code J3590 to report Tzield™.</td>
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<tr>
<td>05/01/23</td>
<td>Coding update. Added new HCPCS code C9149.</td>
</tr>
<tr>
<td>05/01/23</td>
<td>Annual Review, approved April 11, 2023. Added insulin degludec and Rezvoglar (insulin glargine-aglr) to policy as non-preferred long-acting insulins. Updated initial and re-authorization duration for all drugs listed in the policy except Tzield to up to 3 years.</td>
</tr>
<tr>
<td>07/01/23</td>
<td>Coding update. Added new HCPCS codes J1813, J1814, and J9381. Termed HCPC code C9149.</td>
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</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2023 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross (Premera) complies with applicable Federal and Washington state civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, sex, gender identity, or sexual orientation. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability, sex, gender identity, or sexual orientation. Premera provides free aids and services to people with disabilities to communicate effectively with us, such as qualified sign language interpreters and written information in other formats (large print, audio, accessible electronic formats, other formats). Premera provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, contact the Civil Rights Coordinator. If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, sex, gender identity, or sexual orientation, you can file a grievance with: Civil Rights Coordinator — Complaints and Appeals, PO Box 91102, Seattle, WA 98111, Toll free: 855-332-4535, Fax: 425-918-5592, TTY: 711, Email AppealsDepartmentInquiries@Premera.com. You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Ave SW, Room 509F, HHH Building, Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/index.html.


Alaska residents: Contact the Alaska Division of Insurance via email at insurance@alaska.gov, or by phone at 907-269-7900 or 1-800-INSURAK (in-state, outside Anchorage).

Language Assistance

ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 800-722-1471 (TTY: 711).


注意: 您如果使用繁體中文,您可以免費獲得語言援助服務。請致電 800-722-1471 (TTY: 711)。

주의: 한국어를 사용하시는 분들에게는 무료로 상담이 가능합니다. 전화로 800-722-1471 (TTY: 711)으로 문의해 주십시오.


MO LOU SILAFIA: Afaí e te taulata Gagana fa'a Sāmoa, o loi iaiauanauga fesoasoan, e faí fa e leai se tootog, mo oe. Telefoni mai: 800-722-1471 (TTY: 711).

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УВАГА! Якщо ви розмовляєте українською мовою, ви можете звернутися до безкоштовної служби мовоної підтримки. Телефонуйте за номером 800-722-1471 (телетайн: 711).

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