PREMERA HMO

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PHARMACY / MEDICAL POLICY – 5.01.569

Pharmacotherapy of Type 1 and Type 2 Diabetes Mellitus

Effective Date:	Apr. 1, 2025	RELATED MEDICAL POLICIES / GUIDELINES:	
Last Revised:	Mar. 11, 2025	5.01.648	Insulin Therapy
Replaces:	N/A	5.01.646	SGLT2 Inhibitors

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

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 1 and type 2. In type 1 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 1 diabetes is usually diagnosed in children and young adults. In type 2 diabetes, people can still make insulin, but their bodies don't respond well to it. This is known as insulin resistance. Type 2 diabetes can be diagnosed at any age and can be affected and modified by a number of factors, such as diet and exercise and other health conditions. It can also be a side-effect of certain drugs. Type 2 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.

Policy Coverage Criteria

Documentation in the form of clinical chart notes is required for a review of all non-preferred agents.

Metformin					
GLP-1	**GIP-GLP-1**	**Insulin-GLP-1**	**DPP-4**	**DPP-4-Biguanide**	**DPP-4-SGLT-2**
Preferred					
• Ozempic • Rybelsus • Trulicity • Victoza	• Mounjaro	• Soliqua • Xultophy	• Januvia • Tradjenta	• Janumet • Janumet XR • Jentadueto • Jentadueto XR	• Glyxambi • Qtern • Trijardy XR
Non-Preferred					
			• Nesina • Alogliptin • Onglyza • Oseni • Alogliptin-Pioglitazone • Sitagliptin • Zituvio	• Alogliptin / Metformin • Kazano • Kombiglyze XR • Sitagliptin-metformin • Zituvimet • Zituvimet XR	• Steglujan

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Select the link below to view coverage criteria for non-preferred products:

CD3-Directed Antibody (Intravenous)

Insulin and Injectable Noninsulin Combination Products

Injectable/Oral Noninsulin Products

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

CD3-Directed Antibody (Intravenous)

Medical Necessity
CD3-Directed Antibody (Intravenous)

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 (Related Information) when the following criteria are met:

- The individual is aged 8 years or older

AND

- 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

AND

- Tzield (teplizumab-mzwv) is administered as a once daily infusion for 14 consecutive days

AND

- Tzield (teplizumab-mzwv) 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 and Injectable Noninsulin Combination Products

Medical Necessity
Preferred Injectable
Insulin and Glucagon-like Peptide-1 (GLP-1) Receptor Agonists

Considered medically necessary when the individual has a diagnosis of type 2 diabetes (Related Information), has had an adequate trial of or a contraindication to metformin, and will not be used in combination with another GLP-1 or GIP/GLP-1 receptor agonist:

Medical Necessity
Preferred Injectable
Insulin and Glucagon-like Peptide-1 (GLP-1) Receptor Agonists
• Soliqua (insulin glargine-lixisenatide) • Xultophy (insulin degludec-liraglutide)

Injectable/Oral Noninsulin Products

Medical Necessity	
Preferred	**Non-preferred**
Glucagon-like Peptide-1 (GLP-1) Receptor Agonists	

Considered medically necessary when the individual has a diagnosis of type 2 diabetes, has had an adequate trial of or a contraindication to metformin, and will not be used in combination with another GLP-1 or GIP/GLP-1 receptor agonist:
• Ozempic (semaglutide injectable)
• Rybelsus (semaglutide oral)
• Trulicity (dulaglutide)
• Victoza (liraglutide)
	Brand liraglutide may be considered medically necessary when the individual has a diagnosis of type 2 diabetes (Related Information), will not be used in combination with another GLP-1 or GIP/GLP-1 receptor agonist, and has had an adequate trial of or a contraindication to:
	• Metformin
	AND
	• Has had an adequate trial of TWO of the following:
	  ○ Mounjaro (tirzepatide)
	  ○ Ozempic (semaglutide injectable)
	  ○ Rybelsus (semaglutide oral)
	  ○ Trulicity (dulaglutide)
	  ○ Victoza (liraglutide)

Glucose-Dependent Insulinotropic Polypeptide (GIP) Receptor and Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists	
Considered medically necessary when the individual has a diagnosis of type 2 diabetes, has had an adequate trial of or a contraindication to metformin, and will not	**N/A**

Medical Necessity	
Preferred	**Non-preferred**
be used in combination with another GLP-1 or GIP/GLP-1 receptor agonist: • Mounjaro (tirzepatide)	
Amylin Mimetics	
Considered medically necessary when the individual has a diagnosis of type 1 or type 2 diabetes (Related Information) and be concurrently receiving insulin therapy: • Symlin (pramlintide)	**N/A**
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors	

Considered medically necessary when the individual has a diagnosis of type 2 diabetes (Related Information), has had an adequate trial of or a contraindication to metformin, and will not be used in combination with another DPP-4 inhibitor:
• Januvia (sitagliptin)
• Tradjenta (linagliptin)
	Nesina (alogliptin), alogliptin, Onglyza (saxagliptin), Oseni (alogliptin/pioglitazone), alogliptin/pioglitazone, sitagliptin, and Zituvio (sitagliptin) may be considered medically necessary when the individual has a diagnosis of type 2 diabetes (Related Information), will not be used in combination with another DPP-4 inhibitor, and has had an adequate trial of or a contraindication to metformin:
	AND
	• Has had an adequate trial of 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	
Considered medically necessary when the individual has a diagnosis of type 2 diabetes (Related Information), has had an adequate	**Kazano (alogliptin-metformin), Kombiglyze XR (saxagliptin-metformin extended release), alogliptin-metformin, sitagliptin-**

Medical Necessity	
Preferred	**Non-preferred**
trial of or a contraindication to metformin, and will not be used in combination with another DPP-4 inhibitor: • Janumet (sitagliptin-metformin) • Janumet XR (sitagliptin-metformin extended release) • Jentadueto (linagliptin-metformin) • Jentadueto XR (linagliptin-metformin extended-release)	**metformin, Zituvimet (sitagliptin-metformin), and Zituvimet XR (sitagliptin-metformin extended-release) may be considered medically necessary when the individual has a diagnosis of type 2 diabetes (Related Information), will not be used in combination with another DPP-4 inhibitor, and has had an adequate trial of or a contraindication to metformin:** **AND** • Has had an adequate trial of 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 SGLT-2 Combination	
Considered medically necessary when the individual has a diagnosis of type 2 diabetes (Related Information), will not be used in combination with another SGLT2 inhibitor or DPP-4 inhibitor, and has had an adequate trial of or a contraindication to metformin: • Glyxambi (empagliflozin-linagliptin) • Qtern (dapagliflozin-saxagliptin) • Trijardy XR (empagliflozin-linagliptin-metformin)	**Steglujan (ertugliflozin-sitagliptin) may be considered medically necessary when the individual has a diagnosis of type 2 diabetes (Related Information), will not be used in combination with another SGLT2 inhibitor DPP-4 inhibitor, and has had an adequate trial or contraindication to metformin:** **AND** • Has had an adequate trial of one of the following: ○ Glyxambi (empagliflozin-linagliptin) ○ Qtern (dapagliflozin-saxagliptin) ○ Trijardy XR (empagliflozin-linagliptin-metformin)

Drug	Investigational
As listed	**Re-authorization of Tzield (teplizumab-mzwv) beyond the once daily infusion for 14 consecutive days is considered investigational.** **The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.** **All other uses of the drugs for conditions not listed in this policy 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. • Use of Ozempic (semaglutide) for weight management is considered investigational. Please see Wegovy (semaglutide) criteria in **Policy 5.01.621** Drugs for Weight Management. • Use of Mounjaro (tirzepatide) for weight management is considered investigational. Please see Zepbound (tirzepatide) criteria in **Policy 5.01.621** Drugs for Weight Management.

Drug	Not Medically Necessary
As listed	**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.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Tzield (teplizumab-mzwv) will be approved for a once daily infusion for 14 consecutive days.** **Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months.**

Length of Approval	
Approval	**Criteria**
	All other reviews for all other drugs listed in policy may be approved up to 3 years.
Re-authorization criteria	**Re-authorization of Tzield (teplizumab-mzwv) beyond the once daily infusion for 14 consecutive days is considered investigational.** **Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.** **All other reviews for re-authorization of all other drugs listed in policy may be approved up to 3 years as long as the drug-specific coverage criteria are met, and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

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

Code	Description
HCPC	
J9381	Injection, teplizumab-mzwv (Tzield), 5 mcg

Related Information

Benefit Application

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

Criteria for Diagnosis of Diabetes in Nonpregnant Individuals[25]

Criteria for Diagnosis of Diabetes in Nonpregnant Individuals
A1C ≥6.5% (≥48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG ≥126 mg/dL (≥7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (≥11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (≥11.1 mmol/L). Random is any time of the day without regard to time since previous meal.

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NGSP, National Glycohemoglobin Standardization Program; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results obtained at the same time (e.g., A1C and FPG) or at two different time points.

Staging of Type 1 Diabetes[25]

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• Autoimmunity • Overt hyperglycemia • Symptomatic
Diagnostic Criteria	• Multiple islet autoantibodies • No IGT or IFG	• Islet autoantibodies (usually multiple) • Dysglycemia: IFG and/or IGT • FPG 100-125 mg/dL (5.6-6.9 mmol/L) • 2-h PG 140-199 mg/dL (7.8-11.0 mmol/L)	• Autoantibodies may become absent • Diabetes by **standard criteria**

Stage 1		Stage 2	Stage 3
		• A1C 5.7-6.4% (39-47 mmol/mol) or ≥10% increase in A1C	

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose. Alternative additional stage 2 diagnostic criteria of 30-, 60-, or 90-min plasma glucose on oral glucose tolerance test ≥200 mg/dL (≥11.1 mmol/L) and confirmatory testing in those aged ≥18 years have been used in clinical trials.

Evidence Review

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, Ozempic, Trulicity, and Victoza are available as SQ injections with Rybelsus being available as an oral tablet. 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. 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. 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 1 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/m^2, the consistent positive results in disparate treatment groups suggest 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. Reduction 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 a 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 HbA1capproximately -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.

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)

For details on the secondary outcomes (transient ischemic attack, coronary revascularization, hospitalization for unstable angina pectoris, hospitalization for heart failure, microvascular events, such as retinopathy and nephropathy, and safety and adverse events information, please refer to The New England Journal of Medicine article available at: **http://www.nejm.org/doi/full/10.1056/NEJMoa1603827** (Accessed January 2, 2025)

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 Type 2 Diabetes Management Algorithm (2023)

Goals for Glycemic Control of Type 1 and Type 2 Diabetes Mellitus	
A1C	Safe and achievable for most individuals: ≤ 6.5% Individual specific characteristics that would recommend a less stringent A1C target (eg, 7%-8%), including the following: Limited life expectancy, history of severe hypoglycemia, hypoglycemia unawareness, advanced renal disease, other severe comorbid conditions with a high risk of cardiovascular disease events, long type 2 diabetes duration with difficulty to attain an A1C goal, or prohibitive cognitive and/or psychological status
Fasting Blood Glucose	<110 mg/dL
2-Hour Postprandial Glucose	<140 mg/dL

US 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

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History

Date	Comments
08/31/16	New Policy, add to Prescription Drug section. Policy effective date is October 1, 2016.
12/01/16	Interim Review, approved November 8, 2016. New GLP-1 agent, called Adlyxin (lixisenatide) was added to the non-preferred GLP-1 agonist criteria.
02/10/17	Annual Review, approved January 10, 2017. Added new agents Xultophy and Soliqua to the policy. Updated corresponding description and references sections.
04/01/17	Interim Review, approved March 14, 2017. Updated formulary status for Xultophy and Soliqua, previously non-preferred.
10/01/17	Interim Review, approved September 12, 2017. Added Symlin (pramlintide) and updated description and reference sections.
11/01/17	Interim Review, approved October 19, 2017. Updated criteria if metformin is contraindicated.
11/07/17	Minor formatting updates.
01/01/18	Interim Review, approved December 20, 2017. Added Ozempic as a preferred injectable noninsulin product.
03/01/18	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.
04/01/18	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.
04/01/19	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.

Date	Comments
08/01/19	Interim Review, approved July 25, 2019. Added Basaglar (insulin glargine), Fiasp (insulin aspart), insulin lispro and Bydureon BCise (exenatide extended-release) to policy.
11/01/19	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.
01/01/20	Interim Review, approved December 17, 2019. Added Rybelsus as a preferred GLP-1 receptor agonist.
02/01/20	Interim Review, approved January 23, 2020. Added authorized generic for insulin aspart and insulin aspart protamine mix 70/3 as preferred.
08/01/20	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 (linaglitpin + 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 (canagliflozin + metformin), Invokamet XR (canagliflozin + metformin extended-release) and Segluromet (ertugliflozin + metformin) as non-preferred and Synjardy (empagliflozin + metformin), Synjardy XR (empagliflozin + metformin extended-release), and Xigduo XR (dapagliflozin + metformin extended-release) as preferred. For DPP-4 and SGLT-2 Combination medications moved Steglujan (ertugliflozin + sitagliptin) to non-preferred and added coverage criteria for Trijardy XR (empagliflozin + linagliptin + metformin) as non-preferred. Updated coverage criteria for all non-preferred DPP-4 and SGLT-2 Combination medications.
09/01/20	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.
12/01/20	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.
03/01/21	Annual Review, approved February 18, 2021. Changed Soliqua (insulin glargine+lixisenatide) to a preferred insulin and GLP-1 receptor agonist product.

Date	Comments
	Removed reference to Tanzeum (albiglutide) from policy as the drug was discontinued by manufacturer.
09/01/21	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.
05/01/22	Annual Review, approved April 25, 2022. Added brand Insulin Glargine (glargine-yfgn) as a non-preferred long–acting insulin.
07/01/22	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.
10/01/22	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 "patient" to "individual" for standardization.
11/01/22	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.
03/01/23	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 Brenzavvy (bexagliflozin) to policy as a non-preferred SGLT2 inhibitor. Added HCPC code J3590 to report Tzield.
04/01/23	Coding update. Added new HCPCS code C9149.
05/01/23	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.
07/01/23	Coding update. Added new HCPCS codes J1813, J1814, and J9381. Termed HCPC code C9149.
03/01/2024	Interim Review, approved February 13, 2024. Added brand bexagliflozin and brand dapagliflozin to policy as a non-preferred SGLT2 inhibitor. Added Zituvio (sitagliptin) to policy as a non-preferred DPP-4 inhibitor. Added insulin glargine to policy as a non-preferred insulin. Added Zituvimet (sitagliptin-metformin) to policy as a non-preferred DPP-4 inhibitor/biguanide combination. Removed Adlyxin (lixisenatide) from the policy as it has been withdrawn from the market. Added brand dapagliflozin-metformin to policy as a non-preferred SGLT2 inhibitor/biguanide combination.
08/01/24	Annual Review, approved July 8, 2024. Added supplemental diabetes diagnostic criteria in the Related Information section.
11/01/24	Interim Review, approved October 8, 2024. Added brand liraglutide as a non-preferred GLP-1 agonist.

Date	Comments
01/01/25	Interim Review, approved December 23, 2024. Moved Novolog, Fiasp, insulin aspart, Humalog, insulin lispro, Apidra, Admelog, Admelog Solostar, Lyumjev, Novolin R, Humulin R, Novolin R, Humulin N, Novolin Mix 70/30, Humulin Mix 70/30, Novolog Mix 70/30, insulin aspart protamine-insulin aspart mix 70/30, Humalog Mix 75/25, Humalog Mix 50/50, Lantus, Levemir, Toujeo, Tresiba, Basaglar, insulin degludec, insulin glargine (insulin glargine), insulin glargine (insulin glargine-yfgn), Rezvoglar, and Semglee from Policy 5.01.569 to 5.01.648. Moved Farxiga, Jardiance, Brenzavvy, brand bexagliflozin, brand dapagliflozin, Invokana, Steglatro, Synjardy, Synjardy XR, Xigduo XR, brand dapagliflozin-metformin, Invokamet, Invokamet XR, and Segluromet from Policy 5.01.569 to 5.01.646. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.
02/01/25	Annual Review, approved January 14, 2025. Added brand sitagliptin as a non-preferred DPP-4 inhibitor. Added brand sitagliptin-metformin and Zituvimet XR (sitagliptin-metformin extended-release) as non-preferred DPP-4 and biguanide combinations. Removed Bydureon as product has been discontinued (only Bydureon BCise is available). Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Removed HCPCS codes J1813, J1814 and J3590.
04/01/25	Interim Review, approved March 11, 2025. Removed Bydureon BCise and Byetta as both products have been withdrawn from the market. Updated Ozempic, Rybelsus, Mounjaro, Trulicity, Victoza, brand liraglutide, Soliqua, and Xultophy coverage criteria to require that use will not be in combination with another GLP-1 or GIP/GLP-1 receptor agonist. Updated Januvia, Tradjenta, Nesina, alogliptin, Onglyza, Oseni, alogliptin-pioglitazone, sitagliptin, Zituvio, Janumet, Janumet XR, Jentadueto, Jentadueto XR, Kazano, Kombiglyze XR, alogliptin-metformin, sitagliptin-metformin, Zituvimet, and Zituvimet XR coverage criteria to require that use will not be in combination with another DPP-4 inhibitor. Updated Glyxambi, Qtern, Trijardy XR, and Steglujan coverage criteria to require that use will not be in combination with another DPP-4 inhibitor or SGLT2 inhibitor.

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.