

PHARMACY / MEDICAL POLICY – 5.01.569

Pharmacotherapy of Type I and Type II Diabetes Mellitus

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None

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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 as 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.

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	SGLT-2	SGLT-2 + Biguanide	DPP-4 +SGLT-2
Preferred							
Bydureon	Mounjaro	Soliqua	Januvia	Janumet	Jardiance	Synjardy	Glyxambi
Byetta		Xultophy	Tradjenta	Janumet XR	Farxiga	Synjardy XR	Qtern
Ozempic				Jentadueto		Xigduo XR	Trijardy XR
Rybelsus				Jentadueto XR			
Trulicity							
Victoza							
Non-Preferred							
			Nesina	Alogliptin / Metformin	Brenzavvy	Invokamet	Steglujan
			Alogliptin	Kazano	Invokana	Invokamet XR	
			Onglyza	Kombiglyze XR	Steglatro	Segluromet	
			Oseni				
			Alogliptin / Pioglitazone				



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

[CD3-Directed Antibody \(Intravenous\)](#)

[Insulin Products \(Vials and Prefilled Pens\)](#)

[Insulin and Injectible 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)

Medical Benefit
CD3-Directed Antibody (Intravenous)
<ul style="list-style-type: none">Tzield (teplizumab-mzwv) <p>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 (Related Information) when the following criteria are met:</p> <ul style="list-style-type: none">Individual is \geq 8 years of age <p>AND</p> <ul style="list-style-type: none">Individual is at risk of developing T1D as documented by both of the following:<ul style="list-style-type: none">Presence of \geq 2 autoantibodies<ul style="list-style-type: none">Glutamic acid decarboxylase 65 (GAD) autoantibodyInsulin 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)

Preferred Insulin	Non-preferred Insulin
Rapid-Acting Insulin	
<ul style="list-style-type: none"> • Novolog (aspart) • Fiasp (aspart) • Insulin aspart <p>Coverage Criteria: No prior authorization required</p>	<ul style="list-style-type: none"> • Humalog (lispro) • Insulin lispro • Apidra (glulisine) • Admelog (lispro) • Admelog Solostar (lispro) • Lyumjev (lispro) <p>Coverage Criteria: For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type I or type II diabetes (Related Information), 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	
<ul style="list-style-type: none"> • Novolin R <p>Coverage Criteria: No prior authorization required</p>	<ul style="list-style-type: none"> • Humulin R <p>Coverage Criteria: For the above drug to be considered medically necessary, individual needs to have a diagnosis of type I or type II diabetes (Related Information), and have a contraindication or intolerance</p>



Preferred Insulin	Non-preferred Insulin
	to the preferred insulin OR this insulin product was ineffective in reducing A1C to goal after three months of therapy.
Intermediate-Acting NPH Insulin	
<ul style="list-style-type: none"> Novolin N <p>Coverage Criteria: No prior authorization required</p>	<ul style="list-style-type: none"> Humulin N <p>Coverage Criteria: For the above drug to be considered medically necessary, individual needs to have a diagnosis of type I or type II diabetes (Related Information), 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>
Mix of Intermediate-Acting NPH and Regular (Short-Acting) Insulin	
<ul style="list-style-type: none"> Novolin Mix 70/30 <p>Coverage Criteria: No prior authorization required</p>	<ul style="list-style-type: none"> Humulin Mix 70/30 <p>Coverage Criteria: For the above drug to be considered medically necessary, individual needs to have a diagnosis of type I or type II diabetes (Related Information), 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>
Mix of Intermediate Insulin Lispro Protamine + Rapid-acting Insulin Lispro and Mix of Intermediate-acting Insulin Aspart Protamine + Rapid-acting Insulin Aspart	
<ul style="list-style-type: none"> Novolog Mix 70/30 Insulin aspart protamine + insulin aspart mix 70/30 <p>Coverage Criteria: No prior authorization required</p>	<ul style="list-style-type: none"> Humalog Mix 75/25 Humalog Mix 50/50 <p>Coverage Criteria: For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type I or type II diabetes (Related Information), and have a contraindication or intolerance to the preferred insulin OR this insulin product was ineffective in</p>



Preferred Insulin	Non-preferred Insulin
	reducing A1C to goal after three months of therapy.
Long-Acting Insulin	
<ul style="list-style-type: none"> • Lantus (glargine) • Levemir (detemir) • Toujeo (glargine) • Tresiba (degludec) <p>Coverage Criteria: No prior authorization required</p>	<ul style="list-style-type: none"> • Basaglar (glargine) • Insulin Degludec (degludec) • Insulin Glargine (glargine) • Insulin Glargine (glargine-yfgn) • Rezvoglar (glargine-aglr) • Semglee (glargine-yfgn) <p>Coverage Criteria: For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type I or type II diabetes (Related Information), 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.</p>

Insulin and Injectable Noninsulin Combination Products

Preferred Injectable
Insulin and Glucagon-like Peptide-1 (GLP-1) Receptor Agonists
<ul style="list-style-type: none"> • Soliqua (insulin glargine+lixisenatide) • Xultophy (insulin degludec+liraglutide) <p>Coverage Criteria: For the above drugs to be considered medically necessary, the individual needs to have a diagnosis of type II diabetes (Related Information), and have an adequate trial of:</p> <ul style="list-style-type: none"> • Metformin (unless contraindicated)

Injectable/Oral Noninsulin Products

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



Preferred	Non-preferred
<ul style="list-style-type: none"> • Bydureon and Bydureon BCise (exenatide extended-release) • Byetta (exenatide) • Ozempic (semaglutide injectable) • Rybelsus (semaglutide oral) • Trulicity (dulaglutide) • Victoza (liraglutide) <p>Coverage Criteria: For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type II diabetes (Related Information), and have an adequate trial of:</p> <ul style="list-style-type: none"> • Metformin (unless contraindicated) 	<ul style="list-style-type: none"> • Brand liraglutide <p>Coverage Criteria: For the above drugs to be considered medically necessary, the individual needs to have a diagnosis of type II diabetes (Related Information), and have an adequate trial of:</p> <ul style="list-style-type: none"> • Metformin (unless contraindicated) <p>AND</p> <ul style="list-style-type: none"> • Two of the following: <ul style="list-style-type: none"> ○ Bydureon/Bydureon BCise (exenatide extended-release) or Byetta (exenatide) ○ 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	
<ul style="list-style-type: none"> • Mounjaro (tirzepatide) <p>Coverage Criteria: For the above drug to be considered medically necessary, the individual needs to have a diagnosis of type II diabetes (Related Information), and have an adequate trial of:</p> <ul style="list-style-type: none"> • Metformin (unless contraindicated) 	
Amylin Mimetics	
<ul style="list-style-type: none"> • Symlin (pramlintide) <p>Coverage Criteria: For the above drug to be considered medically necessary, individual needs:</p> <ul style="list-style-type: none"> • To have a diagnosis of type I or type II diabetes (Related Information) 	N/A



Preferred	Non-preferred
<p>AND</p> <ul style="list-style-type: none"> Be concurrently receiving insulin therapy 	
<p>Dipeptidyl Peptidase IV Inhibitors (DPP-4)</p>	
<ul style="list-style-type: none"> Januvia (sitagliptin) Tradjenta (linagliptin) <p>Coverage Criteria: For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type II diabetes (Related Information), and have an adequate trial of:</p> <ul style="list-style-type: none"> Metformin (unless contraindicated) 	<ul style="list-style-type: none"> Nesina (alogliptin) alogliptin Onglyza (saxagliptin) Oseni (alogliptin/pioglitazone) alogliptin/pioglitazone Zituvio (sitagliptin) <p>Coverage Criteria: For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type II diabetes (Related Information), and have an adequate trial of:</p> <ul style="list-style-type: none"> Metformin (unless contraindicated) <p>AND</p> <ul style="list-style-type: none"> Two of the following: <ul style="list-style-type: none"> Januvia (sitagliptin) Janumet (sitagliptin + metformin) Janumet XR (sitagliptin + metformin extended release) Jentadueto (linagliptin + metformin) Jentadueto XR (linagliptin + metformin extended-release) Tradjenta (linagliptin)
<p>DPP-4 and Biguanide Combination</p>	
<ul style="list-style-type: none"> Janumet (sitagliptin + metformin) Janumet XR (sitagliptin + metformin extended release) Jentadueto (linagliptin + metformin) Jentadueto XR (linagliptin + metformin extended-release) <p>Coverage Criteria: For the above drugs to be considered medically necessary, individual</p>	<ul style="list-style-type: none"> Kazano (alogliptin + metformin) Kombiglyze XR (saxagliptin + metformin extended release) alogliptin/metformin Zituvimet (sitagliptin + metformin) <p>Coverage Criteria: For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type II diabetes</p>



Preferred	Non-preferred
<p>needs to have a diagnosis of type II diabetes (Related Information), and have an adequate trial of:</p> <ul style="list-style-type: none"> • Metformin (unless contraindicated) 	<p>(Related Information), and have an adequate trial of:</p> <ul style="list-style-type: none"> • Metformin (unless contraindicated) <p>AND</p> <ul style="list-style-type: none"> • Two of the following: <ul style="list-style-type: none"> ○ Januvia (sitagliptin) ○ Janumet (sitagliptin + metformin) ○ Janumet XR (sitagliptin + metformin extended release) ○ Jentadueto (linagliptin + metformin) ○ Jentadueto XR (linagliptin + metformin extended-release) ○ Tradjenta (linagliptin
Sodium-Glucose Cotransporter 2 Inhibitors (SGLT-2)	
<ul style="list-style-type: none"> • Jardiance (empagliflozin) • Farxiga (dapagliflozin) <p>Coverage Criteria: For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type II diabetes (Related Information), and have an adequate trial of:</p> <ul style="list-style-type: none"> • Metformin (unless contraindicated) 	<ul style="list-style-type: none"> • Brenzavvy (bexagliflozin)/brand bexagliflozin • Brand dapagliflozin • Invokana (canagliflozin) • Steglatro (ertugliflozin) <p>Coverage Criteria: For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type II diabetes (Related Information), and have an adequate trial of:</p> <ul style="list-style-type: none"> • Metformin (unless contraindicated) <p>AND</p> <ul style="list-style-type: none"> • Two of the following: <ul style="list-style-type: none"> ○ Farxiga (dapagliflozin) ○ Jardiance (empagliflozin) ○ Synjardy (empagliflozin + metformin) ○ Synjardy XR (empagliflozin + metformin extended-release) ○ Xigduo XR (dapagliflozin + metformin extended-release)
SGLT-2 and Biguanide Combination	
<ul style="list-style-type: none"> • Synjardy (empagliflozin + metformin) 	<ul style="list-style-type: none"> • Brand dapagliflozin-metformin



Preferred	Non-preferred
<ul style="list-style-type: none"> Synjardy XR (empagliflozin + metformin extended-release) Xigduo XR (dapagliflozin + metformin extended-release) <p>Coverage Criteria: For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type II diabetes (Related Information), and have an adequate trial of:</p> <ul style="list-style-type: none"> Metformin (unless contraindicated) 	<ul style="list-style-type: none"> Invokamet (canagliflozin + metformin) Invokamet XR (canagliflozin + metformin extended-release) Segluromet (ertugliflozin + metformin) <p>Coverage Criteria: For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type II diabetes (Related Information), and have an adequate trial of:</p> <ul style="list-style-type: none"> Metformin (unless contraindicated) <p>AND</p> <ul style="list-style-type: none"> Two of the following: <ul style="list-style-type: none"> Farxiga (dapagliflozin) Jardiance (empagliflozin) Synjardy (empagliflozin + metformin) Synjardy XR (empagliflozin + metformin extended-release) Xigduo XR (dapagliflozin + metformin extended-release)
DPP-4 and SGLT-2 Combination	
<ul style="list-style-type: none"> Glyxambi (empagliflozin + linagliptin) Qtern (dapagliflozin + saxagliptin) Trijardy XR (empagliflozin + linagliptin + metformin) <p>Coverage Criteria: For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type II diabetes (Related Information), and have an adequate trial of:</p> <ul style="list-style-type: none"> Metformin (unless contraindicated) 	<ul style="list-style-type: none"> Steglujan (ertugliflozin + sitagliptin) <p>Coverage Criteria: For the above drugs to be considered medically necessary, individual needs to have a diagnosis of type II diabetes (Related Information), and have an adequate trial of:</p> <ul style="list-style-type: none"> Metformin (unless contraindicated) <p>AND</p> <ul style="list-style-type: none"> One of the following: <ul style="list-style-type: none"> Glyxambi (empagliflozin + linagliptin) Qtern (dapagliflozin + saxagliptin) Trijardy XR (empagliflozin + linagliptin + metformin)



Drug	Investigational
As listed	<p>Future re-authorization of Tzield (teplizumab-mzwv) beyond the once daily infusion for 14 consecutive days is considered investigational.</p> <p>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.</p> <ul style="list-style-type: none"> • 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.

Drug	Not Medically Necessary
As listed	<p>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.</p>

Length of Approval	
Approval	Criteria
Initial authorization	<p>Tzield (teplizumab-mzwv) will be approved for a once daily infusion for 14 consecutive days.</p> <p>All other drugs listed in policy may be approved up to 3 years.</p>
Re-authorization criteria	<p>Future re-authorization of Tzield (teplizumab-mzwv) beyond the once daily infusion for 14 consecutive days is considered investigational.</p> <p>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.</p>



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	
J1813	Insulin (Lyumjev) for administration through DME (i.e., insulin pump) per 50 units
J1814	Insulin (Lyumjev), per 5 units
J3590	Unclassified biologics (use to report Tzield)
J9381	Injection, teplizumab-mzww, (Tzield) 5 mcg

Related Information

Benefit Application

Tzield (teplizumab-mzww) are 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 Individuals³¹

Criteria for Diagnosis of Diabetes in Nonpregnant Individuals

A1C $\geq 6.5\%$ (≥ 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



Criteria for Diagnosis of Diabetes in Nonpregnant Individuals

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 Diabetes³¹

	Stage 1	Stage 2	Stage 3
Characteristics	<ul style="list-style-type: none"> Autoimmunity Normoglycemia Presymptomatic 	<ul style="list-style-type: none"> Autoimmunity Dysglycemia Presymptomatic 	<ul style="list-style-type: none"> Autoimmunity Overt hyperglycemia Symptomatic
Diagnostic Criteria	<ul style="list-style-type: none"> Multiple islet autoantibodies No IGT or IFG 	<ul style="list-style-type: none"> 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) A1C 5.7-6.4% (39-47 mmol/mol) or $\geq 10\%$ increase in A1C 	<ul style="list-style-type: none"> Autoantibodies may become absent Diabetes by standard criteria

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



Insulin Agents

Table 1. Types and Characteristics of Commonly Used Insulin Products

Insulin	Brand Name	Onset of Action	Peak Effect	Duration of Action
Rapid-acting Insulin				
Lispro	Humalog	< 15 minutes	30 to 90 minutes	3 to 5 hours
Aspart	Novolog	< 15 minutes	30 to 90 minutes	3 to 5 hours
Glulisine	Apidra	< 15 minutes	30 to 90 minutes	3 to 5 hours
Short-acting Insulin				
Regular	Humulin R	0.5 to 1 hour	2 to 4 hours	4 to 8 hours
	Novolin R	0.5 to 1 hour	2 to 4 hours	4 to 8 hours
Intermediate-acting Insulin				
NPH	Humulin N	1 to 2 hours		
	Novolin N	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	Levemir	1 to 2 hours	3 to 9 hours	6 to 24 hours *
Glargine	Basaglar	1 to 2 hours	No peak	20 to 24 hours
Glargine	Lantus	1 to 2 hours	No peak	20 to 24 hours
Glargine	Semglee	1 to 2 hours	No peak	20 to 24 hours
Glargine	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 glycosylated 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 greater 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 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=38/3years). 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 October 16, 2024).

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)

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 June 13, 2024)

The results of this trial suggest that liraglutide has lower rates of CV events and death from 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: $\leq 6.5\%$ 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

1. The American Association of Clinical Endocrinologists and American College of Endocrinologists (AACE/ACE) Diabetes Resource Center. [Online database]. Available at: <https://www.aace.com/disease-and-conditions/diabetes/type-1-diabetes> Accessed June 13, 2024.



2. American Association of Clinical Endocrinologists and American College of Endocrinologists (AACE/ACE) Comprehensive Type 2 Diabetes Management Algorithm 2023. [Online database]. Available at: <https://pro.aace.com/clinical-guidance/diabetes> Accessed June 13, 2024.
3. U.S. Food and Drug Administration: Emergency Preparedness: Information Regarding Insulin Storage and Switching Between Products in an Emergency. [Online database]: Updated September, 2017. Available at: <http://www.fda.gov/Drugs/EmergencyPreparedness/ucm085213.htm> Accessed June 13, 2024.
4. Dowlat HA, Kuklmann MK, Khatami H, Ampudia-Blasco FJ. Diabetes Obes Metab 2016 Aug; 18(8):737-46 doi: 10.1111/dom.12676. Epub May 2016. Interchangeability among reference insulin analogues and their biosimilars: regulatory framework, study design and clinical implications. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27097592> Accessed June 13, 2024.
5. Weinstock RS, MD, Nathan DM, MD, Mulder JE, MD. General Principles of Insulin therapy in Diabetes Mellitus. UpToDate-Online Database. Updated September 2021. Available at: <http://www.uptodate.com/contents/general-principles-of-insulin-therapy-in-diabetes-mellitus> Accessed June 13, 2024.
6. Plank J, Wutte A, Brunner G, et al. A Direct Comparison of Insulin Aspart and Insulin Lispro in Patients with Type I Diabetes. Diabetes Care. 2002; 25:2053-2057. Available at: <http://care.diabetesjournals.org/content/25/11/2053> Accessed June 13, 2024.
7. Hedman CA, Lindstrom T, Arnqvist HJ. Direct Comparison of Insulin Lispro and Aspart Shows Small Differences in Plasma Insulin Profiles After Subcutaneous Injection in Type 1 Diabetes. Diabetes Care. 2001; 24:1120-1121. Available at: <http://care.diabetesjournals.org/content/24/6/1120> Accessed June 13, 2024.
8. Von Mach MA, et al. Differences in Pharmacokinetics and Pharmacodynamics of Insulin Lispro and Aspart in Healthy Volunteers. Exp Clin Endocrinol Diabetes. 2002; 110:416-419. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12518253> Accessed June 13, 2024.
9. Marso SP, MD, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2016; 375: 311-322, July 28, 2016. Available at: <http://www.nejm.org/doi/full/10.1056/NEJMoa1603827> Accessed June 13, 2024.
10. Package insert for Adlyxin (lixisenatide). Sanofi-Aventis, LLC. Bridgewater, NJ. Revised June 2022.
11. Package insert for Xultophy (insulin degludec and liraglutide). Novo Nordisk, A/S. Bagsvaerd, Denmark. Revised June 2022.
12. Package insert for Soliqua (insulin glargine and lixisenatide). Sanofi-Aventis, U.S. LLC. Bridgewater, NJ. Revised June 2022.
13. Gough SCL, Bode B, Woo V, et al. Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naïve patients with type 2 diabetes. DUAL I. Lancet Diabetes & Endocrinology. (2014). 2(11):885-893.
14. Lingvay I, Perez MF, Garcia-Hernandez P, et al. Effect of insulin glargine up-titration vs insulin degludec/liraglutide on glycated hemoglobin levels in patients with uncontrolled type 2 diabetes: The DUAL V Randomized Clinical Trial. JAMA 2016; 315(9):898-907.
15. Buse JB, Vilsbøll T, Thurman J, et al. Contribution of liraglutide in the fixed-ratio combination of insulin degludec and liraglutide (IDegLira). DUAL II. Diabetes Care. (2014). 37(11):2926-2933.
16. Rodbard HW, Bode BW, Harris SB, et al. Safety and efficacy of insulin degludec/liraglutide added to sulphonylurea alone or to sulphonylurea and metformin in insulin-naïve people with type 2 diabetes: the DUAL IV trial. Diabetic Medicine. (2016). doi: 10.1111/dme.13256
17. Hampp C, Borders-Hemphill V, Moeny DG, Wysowski DK. Use of antidiabetic drugs in the U.S., 2003-2012. Diabetes Care. (2014). 37(5): 1367-1374. doi: 10.2337/dc13-2289
18. Aroda VR, Bailey TS, Carious B, et al. Effect of adding insulin degludec to treatment in patients with type 2 diabetes inadequately controlled with metformin and liraglutide: a double-blind randomized controlled trial (BEGIN: ADD TO GLP-1 study). Diabetes Obes Metab. (2016). 18(7):663-670. doi: 10.1111/dom.12661
19. Weinzimer SA, Sherr JL, Cengiz E, et al. Effect of pramlintide on prandial glycemic excursions during closed-loop control in adolescents and young adults with type 1 diabetes. Diabetes Care. 2012 Oct;35(10):1994-9. Epub 2012 Jul 18.



20. Hollander PA, Levy P, Fineman MS, et al. Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care*. 2003;26(3):784.
21. Hollander P, Maggs DG, Ruggles JA, et al. Effect of pramlintide on weight in overweight and obese insulin-treated type 2 diabetes patients. *Obes Res*. 2004;12(4):661.
22. Ceriello A, Lush CW, Darsow T, et al. Pramlintide reduced markers of oxidative stress in the postprandial period in patients with type 2 diabetes. *Diabetes Metab Res Rev*. 2008;24(2):103.
23. Qiao, Yong-Chao, et al. Efficacy and safety of pramlintide injection adjunct to insulin therapy in patients with type 1 diabetes mellitus: a systematic review and meta-analysis. *Oncotarget*, 2017, Vol. 8, (No. 39), pp: 66504-66515.
24. Lin GA, Brouwer E, Nikitin D, Moradi A, Chen Y, Herron-Smith S, Hansen RN, Pearson SD, Campbell JD. Tirzepatide for Type 2 Diabetes; Draft Evidence Report. Institute for Clinical and Economic Review, November 9, 2021.
25. Frias, JP. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J Med*. 2021;385: 503-15. DOI: 10.1056/NEJMoa2107519
26. Bellin MD, et al. Transplant strategies for type 1 diabetes: whole pancreas, islet and porcine beta cell therapies. *Diabetologia* 2020;63(10):2049-2056. doi:10.1007/s00125-020-05184-7
27. Bertuzzi F, et al. Brittle type 1 diabetes mellitus *Curr Med Chem*. 2007;14(16):1739-1744. doi:10.2174/092986707781058922
28. de Klerk E, et al. Stem cell-based clinical trials for diabetes mellitus. *Front Endocrinol (Lausanne)*. 2021;12:631463. doi:10.3389/fendo.2021.631463
29. Diabetes UK. Islet cell transplants for type 1 diabetes. <https://www.diabetes.org.uk/guide-to-diabetes/managing-your-diabetes/treating-your-diabetes/islet-cell-transplants> Accessed November 3, 2023.
30. ElSayed NA, et al. 6. Glycemic Targets: Standards of Care in Diabetes—2023. *Diabetes Care*. 2023;46(Suppl 1):S97–S110. doi:10.2337/dc23-S006
31. American Diabetes Association Professional Practice Committee; 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2024. *Diabetes Care* 1 January 2024; 47 (Supplement_1): S20–S42. <https://doi.org/10.2337/dc24-S002>
32. Herold KC, Bundy BN, Long SA, et al.; Type 1 Diabetes TrialNet Study Group. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. *N Engl J Med* 2019;381:603-613.
33. Skyler JS, Bakris GL, Bonifacio E, et al. Differentiation of diabetes by pathophysiology, natural history, and prognosis. *Diabetes* 2017;66:241-255.

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.



Date	Comments
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.
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 (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



Date	Comments
	(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. 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-yfng) 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



Date	Comments
	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.

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). ©2024 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.

