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Medication Policy Manual

Policy No: dru750

Topic: Preferred GLP-1 Agonist-Containing Medications for Diabetes

- Mounjaro, tirzepatide
- Ozempic, semaglutide
- Rybelsus, semaglutide
- Trulicity, dulaglutide

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IMPORTANT REMINDER

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

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

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

Description

GLP-1 agonists are medications used for the treatment of conditions such as type 2 diabetes. They resemble the human incretin hormone, glucagon-like-peptide 1 (GLP-1). Use of these medications for weight loss in the absence of coverable medical conditions is generally a benefit not covered by member contracts regardless of medical necessity. In this instance, coverage is defined by benefit contract language.

Policy/Criteria

Most contracts require pre-authorization approval of preferred GLP-1 agonist-containing medications for diabetes prior to coverage.

I. Continuation of therapy (COT): Preferred GLP-1 agonist-containing medications for diabetes may be considered medically necessary for COT when full policy criteria below are met, including quantity limit.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Preferred GLP-1 agonist-containing medications for diabetes (see *Table 1*) may be considered medically necessary when criterion A or B below is met:

A. A diagnosis of type 2 diabetes.

OR

B. Point-of-sale clinical edit criteria are met, including ICD-10 code and/or adjudicated and paid claims in the member's prescription history of the contingent therapy medications listed in *Appendix 1*.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers preferred GLP-1 agonist-containing medications for diabetes coverable only under the pharmacy benefit (as self-administered medications).

B. When pre-authorization is approved, preferred GLP-1 agonist-containing medications for diabetes will be approved in quantities as follows:

TABLE 1: Preferred GLP-1 agonist-containing medications for diabetes

Product	Quantity Limit
Mounjaro (tirzepatide)	Four pens per 28 days
Ozempic (semaglutide)	• One pen per 28 days; **OR** • 30 tablets per 30 days
Rybelsus (semaglutide)	30 tablets per 30 days
Trulicity (dulaglutide)	Four pens per 28 days

C. Authorization **may** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Preferred GLP-1 agonist-containing medications for diabetes are considered not medically necessary and excluded from coverage (under most benefit contracts) when used for weight loss in the absence of coverable conditions.

V. Preferred GLP-1 agonist-containing medications for diabetes are considered investigational when used for any condition other than type 2 diabetes, including, but not limited to:

A. Islet-cell transplantation

B. Type 1 diabetes (T1D) or diabetic ketoacidosis (DKA)

C. In combination with Symlin (pramlintide) or another GLP-1 agonist-containing medication

Position Statement

Summary

- The intent of this policy is to allow for coverage of preferred GLP-1 agonist-containing medications for diabetes when used for type 2 diabetes (T2D).
- Among the GLP-1 agonist-containing medications for diabetes, dulaglutide, semaglutide, and tirzepatide-containing medications are the best value for members.
- Use of these medications for weight loss in the absence of coverable medical conditions is generally a benefit not covered by member contracts regardless of medical necessity. In this instance, coverage is defined by benefit contract language.
- The safety and effectiveness of GLP-1 agonist-containing medications in conditions other than those included in the coverage criteria (or excluded due to benefit contract language) have not been established.

Background

Type 2 Diabetes (T2D)

- The American Diabetes Association (ADA) Standards of Care in Diabetes recommends the following therapies for adults with T2D. [1]
    - Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of T2D. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals.
    - In adults with T2D and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the first-line treatment regimen should include agents that reduce cardiorenal risk, such as GLP-1 agonists.
    - Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy.

* Weight management is an impactful component of glucose-lowering management in T2D. The glucose-lowering treatment regimen should consider approaches that support weight management goals, including GLP-1 agonists.

Clinical Efficacy

Type 2 Diabetes (T2D)

GLP-1 agonist-containing medications

- GLP-1 agonists lower A1C by up to 1% to 1.5% in those with T2D. [2]
- A multicenter, randomized, double-blind, placebo-controlled trial evaluated the effects of Victoza (liraglutide) compared to placebo on cardiovascular outcomes in patients with T2D at high risk for cardiovascular events. After treatment for approximately 4 years, patients treated with liraglutide plus standard of care had a lower rate of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke compared to patients receiving placebo plus standard of care. [3]
- Similar results were observed in a cardiovascular outcomes trial conducted with Ozempic (semaglutide) injection in patients with T2D at high risk for cardiovascular events. After a mean follow-up of 2 years, patients treated with semaglutide plus standard of care had a significantly lower risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke than those who received placebo plus standard of care. [4]
- In contrast to the trials for Ozempic (semaglutide) and Victoza (liraglutide), the cardiovascular outcomes trial conducted with exenatide plus standard of care trended towards a lower risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke than those who received placebo plus standard of care; however, this trend was not statistically significant. [5]
- In a head-to-head trial comparing Victoza (liraglutide) to Bydureon (exenatide ER), patients receiving liraglutide had a slightly lower average A1C (at end of study) than patients receiving exenatide ER (1.48 vs. 1.28, respectively [$p<0.05$]). This was accompanied by an increase in adverse event experiences by patients receiving liraglutide compared with exenatide ER, including substantially higher rates of nausea (20.4 vs. 9.3%), diarrhea (13.1 vs. 6.1%), and vomiting (10.7 vs. 3.7%). [6]
- In a head-to-head trial comparing Trulicity (dulaglutide) to Byetta (exenatide), patients receiving dulaglutide had a slightly lower average A1C (at end of study) than patients receiving exenatide ER (1.5 vs. 1 respectively [$p<0.001$]). This was accompanied by an increase in adverse event experiences by patients receiving Trulicity (dulaglutide) compared with Byetta (exenatide), including higher rates of diarrhea (11 vs. 6%), and vomiting (17 vs. 11%). [7]
- The efficacy of Ozempic (semaglutide) injection on kidney outcomes was evaluated in a randomized, double-blind, placebo controlled trial in patients (N=3,533) with T2D and chronic kidney disease, Patients had an estimated glomerular filtration rate (eGFR) of 25 to 75 mL/min/1.73 m^2, an HbA1c<10% and be receiving standard of care background therapy, including an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker. Ozempic (semaglutide) was superior to placebo in reducing the

incidence of the primary composite endpoint of a sustained decline in eGFR of ≥50%, sustained eGFR <15 mL/min/1.73 m^2, chronic renal replacement therapy, renal death, CV death (HR 0.76 [95% CI: 0.66 to 0.88] P=0.003). [12]

Glucose-dependent insulinotropic polypeptide (GIP) receptor/GLP-1 agonist [8]

- Mounjaro (tirzepatide) is a dual GIP/GLP-1 receptor agonist with greater in-vitro affinity towards GIP.
- Tirzepatide was studied in two trials compared to placebo, and three trials compared to a long-acting insulin or Ozempic (semaglutide) injection. The patients included in the trials had T2D inadequately controlled on background therapy with metformin, insulins, and/or a sodium-glucose cotransporter-2 inhibitor. Across the trials, patients treated with tirzepatide had significantly greater improvements in A1C vs. the comparator by the end of the study.
- A cardiovascular outcomes trial is currently underway with tirzepatide.

Safety [2,11]

- The most common adverse reactions (reported in ≥5% of patients treated with GLP-1 agonist-containing medications and more commonly than in patients treated with placebo) include upper respiratory tract infection, diarrhea, nausea, vomiting, abdominal pain, decreased appetite, and injection site reaction.
- The long-acting GLP-1 agonist-containing medications have Boxed Warnings regarding the potential risk for medullary thyroid carcinoma. An increased incidence of thyroid C-cell tumors was observed in pre-clinical studies with GLP-1 agonists in animals. The relevance of this effect for humans is unknown. Risk of thyroid cancer is likely a class effect, which has been appreciated with more extensive post-marketing clinical experience.
- The prescribing information for GLP1-agonists lists a warning regarding the risk of acute pancreatitis. Risk of acute pancreatitis is small and likely a class effect, which has been appreciated with more extensive post-marketing clinical experience. A 2014 FDA and European Medicines Agency (EMA) assessment of pancreatic safety of incretin-based drugs stated a causal association between incretin-based drugs and pancreatitis or pancreatic cancer could not be established. Both agencies continue to investigate this safety signal.

Investigational Conditions

- Islet Cell Transplantation
    - Although not evaluated with liraglutide, small-scale trials have evaluated Byetta (exenatide) in the post-transplant management of patients who have received islet-cell transplantation for treatment of type 1 diabetes (T1D). This work is still preliminary, and remains investigational at this time. [9]
- Type 1 Diabetes (T1D) / Diabetic Ketoacidosis (DKA)
    - There are no well-designed, randomized controlled trials that demonstrate a benefit to using GLP-1 agonist-containing medications in T1D. [2]

    - The FDA approved prescribing information for the GLP1-agonists states that they should not be used in patients with T1D or for the treatment of DKA, as it would not be effective in these settings. [2]
    - Although not evaluated with liraglutide, a small exploratory trial evaluated the effect of Byetta (exenatide) compared with insulin in eight children with T1D. While suggestive of a positive effect on post-prandial glucose elevations, clearly larger, well designed clinical trials are necessary to establish the safety and efficacy of exenatide in this population. [10]
- In combination with Symlin (pramlintide) or another GLP-1 agonist.
    - The safety and effectiveness of GLP-1 agonists have not been studied in combination with Symlin (pramlintide) or each other. [2]

Appendix 1: Point-of-Sale Clinical Edits for <u>Preferred</u> GLP-1 Agonist-Containing Medications for Diabetes

Targeted Agents and GPIs (multisource code)	Clinical Edit	Look-Back Time Frame
• Mounjaro, 2717308000**** (M,N,O,Y) • Ozempic, 2717007000**** (M,N,O,Y) • Rybelsus, 2717007000**** (M,N,O,Y) • Trulicity, 2717001500**** (M,N,O,Y)	**<u>Diagnosis</u>** Type 2 Diabetes, E11* **OR**	2 years
	<u>Contingent Therapy</u> Biguanides, 2725********** (M,N,O,Y) **OR** Insulin, 2710********** (M,N,O,Y) **OR** Amylin Analogs, 2715********** (M,N,O,Y) **OR** Sulfonylureas, 2720********** (M,N,O,Y) **OR** Meglitinide Analogues, 2728********** (M,N,O,Y) **OR** Alpha-Glucosidase Inhibitors, 2750********** (M,N,O,Y) **OR** Dipeptidyl Peptidase-4 (DPP-4) Inhibitors, 2755********** (M,N,O,Y) **OR** Insulin Sensitizing Agents, 2760********** (M,N,O,Y) **OR** Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors, 2770********** (M,N,O,Y) **OR** Antidiabetic Combinations, 2799********** (M,N,O,Y)	56 day-supply in 120 days
	<u>Auto-grandfather</u> Mounjaro, 2717308000**** (M,N,O,Y) **OR** Ozempic, 2717007000**** (M,N,O,Y) **OR** Rybelsus, 2717007000**** (M,N,O,Y) **OR** Trulicity, 2717001500**** (M,N,O,Y)	120 days

Appendix 2: Comparison of Reductions in A1C (Monotherapy Only) [2]

Drug	Baseline A1C (%)	Duration of Trial	Mean change from baseline (%)	Placebo Corrected change in A1C (%)
Biguanide				
metformin (Glucophage, generic) up to 2550 mg per day	8.4	29 weeks	-1.4	-1.8
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors				
Nesina (alogliptin) 12.5 mg to 25 mg once daily	7.9	26 weeks	-0.6	-0.6
Tradjenta (linagliptin) 5 mg once daily	7.7 to 8.6	18 to 104 weeks	-0.4 to -0.7	-0.6 to -0.7
Onglyza (saxagliptin) 2.5 mg to 5 mg once daily	7.9 to 8.0	24 weeks	-0.4 to -0.5	-0.6
Januvia (sitagliptin) 100 mg once daily	8.0	18 to 24 weeks	-0.5 to -0.6	-0.6 to -0.8
Glucagon-like Peptide-1 (GLP-1) Agonists				
Trulicity (dulaglutide) up to 1.5 mg weekly (with metformin)	7.6	26 weeks	-0.9 to -1.1	-0.8 to -1.0
Rybelsus (semaglutide) tablets 7 to 14 mg orally once daily	8.0	26 weeks	-1.2 to -1.4	-0.3
Byetta (exenatide) up to 10 mcg twice daily (with metformin)	8.2 to 8.3	30 weeks	-0.4 to -0.8	-0.5 to -0.9
Bydureon (exenatide ER) 2 mg once weekly (with metformin)	8.6	26 weeks	-1.5	N/A†
Victoza (liraglutide) up to 1.8 mg once daily (with metformin)	8.3 to 8.4	26 weeks	-1.0	-1.1
Adlyxin (lixisenatide) up to 20 mcg once daily (with metformin)	8.5	26 weeks	-1.5	N/A†
Ozempic (semaglutide) injection up to 1 mg once weekly (with basal insulin +/- metformin)	8.3 to 8.4	30 weeks	-1.3 to -1.7	-1.1 to -1.6
Mounjaro (tirzepatide) up to 15 mg once weekly	7.9	40 weeks	-1.89 to -2.07	-1.8 to -2.0
Meglitinide				
Prandin (repaglinide) up to 4 mg daily	8.5	12 weeks	-0.6	-1.7
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors				
Invokana (canagliflozin) up to 300 mg once daily	8.01	26 weeks	-1.03	-1.16
Farxiga (dapagliflozin) up to 10 mg once daily	8	24 weeks	-0.9	-0.7
Jardiance (empagliflozin) up to 25 mg once daily	7.9	24 weeks	-0.7	-0.7
Steglatro (ertugliflozin) up to 15 mg once daily	8.2	26 weeks	-0.8 to -1.04	-0.99 to -1.16

Drug	Baseline A1C (%)	Duration of Trial	Mean change from baseline (%)	Placebo Corrected change in A1C (%)
Sulfonylurea				
glimepiride (Amaryl, generic) 8 mg once daily	unknown	14 weeks	unknown	-2.0
Thiazolidinedione (TZD)				
pioglitazone (Actos, generic) 30 mg to 45 mg daily	10.2 to 10.3	26 weeks	-0.3 to -0.9	-1.0 to -1.6

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

Cross References
Non-Incretin Medications for Obesity and Overweight, Medication Policy Manual, Policy No. dru778
Non-Preferred DPP4-Inhibitor-Containing Medications, Medication Policy Manual, Policy No. dru345

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Revision History

Revision Date	Revision Summary
3/16/2026	Added Ozempic (semaglutide) tablets, a new formulation of semaglutide tablets, to policy. Rybelsus (semaglutide) tablets will remain in policy until the existing supply is exhausted.
10/2/2025	No criteria changes with this annual review.
9/19/2024	No criteria changes with this annual review.
6/20/2024	Removed non-preferred GLP-1 agonist-containing medications from policy.
3/21/2024	No changes to intent of policy. Combined preferred and non-preferred GLP-1 agonist-containing medications policies into one and archived dru347.
12/7/2023	Removed Victoza (liraglutide) as a preferred GLP-1 agonist-containing product (added to dru347 Non-Preferred GLP-1 Agonist-Containing Medications policy as a non-preferred product).
7/14/2023	Removed auto-grandfather from Point-of-Sale Clinical Edits (*Appendix 1*) for Mounjaro, Ozempic, Rybelsus, Trulicity, and Victoza (effective 10/1/2023).
6/16/2023	New policy effective 7/15/2023.

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