Clinical Policy: Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

Reference Number: CP.CPA.16
Effective Date: 11.16.16
Last Review Date: 05.18
Line of Business: Commercial

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

The following agents are synthetic glucagon-like peptide-1 (GLP-1) receptor agonists requiring prior authorization: albiglutide (Tanzeum®), dulaglutide (Trulicity®), exenatide ER (Bydureon®), exenatide IR (Byetta®), liraglutide (Victoza®), liraglutide/insulin degludec (Xultophy®), lixisenatide (Adlyxin®), lixisenatide/insulin glargine (Soliqua®), and semaglutide (Ozempic®).

FDA Approved Indication(s)

GLP-1 receptor agonists are indicated as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Victoza is also indicated to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease.

Soliqua and Xultophy should be used in those inadequately controlled on basal insulin (< 60 units daily for Soliqua; < 50 units daily for Xultophy), lixisenatide (for Soliqua only), or liraglutide ≤ 1.8 mg daily (for Xultophy only).

Limitation(s) of use:

- GLP-1 receptor agonists are not recommended as a first-line therapy for patients inadequately controlled on diet and exercise.
- Other than Soliqua and Xultophy which contain insulin, GLP-1 receptor agonists are not a substitute for insulin. They should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis.
- Other than Trulicity, concurrent use with prandial insulin has not been studied and cannot be recommended.
- GLP-1 receptor agonists have not been studied in patients with a history of pancreatitis. Other antidiabetic therapies should be considered.
- Tanzeum and Trulicity are not for patients with pre-existing severe gastrointestinal disease.
- Adlyxin has not been studied in patients with gastroparesis and is not recommended in patients with gastroparesis.

Policy/Criteria

Provider must submit documentation (including such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that GLP-1 receptor agonists are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Type 2 Diabetes Mellitus (must meet all)**:**

1. Diagnosis of type 2 diabetes mellitus;
2. Member meets one of the following (a or b):
   a. Failure of at least a 3 month trial of metformin unless contraindicated or clinically significant adverse effects are experienced;
   b. HbA1c drawn within the past 3 months is ≥ 9%, and concurrent use of metformin unless contraindicated or clinically significant adverse effects are experienced;
3. For Adlyxin, Bydureon, Byetta, Soliqua, Tanzeum, and Xultophy: Failure of Victoza and Trulicity, unless both are contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed: 20 mcg/day for Adlyxin, 2 mg/week for Bydureon, 20 mcg/day for Byetta, 1 mg/week for Ozempic, 60 units/20 mcg/day for Soliqua, 50 mg/week for Tanzeum, 1.5 mg/week for Trulicity, 1.8 mg/day for Victoza, and 50 units/1.8 mg/day for Xultophy.

Approval duration: 6 months (Adlyxin, Ozempic: 2 pens/month; Byetta, Bydureon, Tanzeum, Trulicity, Victoza: 4 vials or pens/month; Soliqua, Xultophy: 6 pens/month)

B. Other diagnoses/indications

1. Refer to CP.CPA.09 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Type 2 Diabetes Mellitus (must meet all)**:**

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed: 20 mcg/day for Adlyxin, 2 mg/week for Bydureon, 20 mcg/day for Byetta, 1 mg/week for Ozempic, 60 units/20 mcg/day for Soliqua, 50 mg/week for Tanzeum, 1.5 mg/week for Trulicity, 1.8 mg/day for Victoza, and 50 units/1.8 mg/day for Xultophy.

Approval duration: Length of Benefit

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to CP.CPA.09 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – CP.CPA.09 or evidence of coverage documents;

B. Other than Byetta, GLP-1 receptor agonists are contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) and multiple endocrine neoplasia syndrome type 2 (MEN 2).

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AACE: American Association of Clinical Endocrinologists
ACE: American College of Endocrinology
ADA: American Diabetes Association
CVD: cardiovascular disease
ER: extended-release
FDA: Food and Drug Administration
GLP-1: glucagon-like peptide-1
HbA1c: glycated hemoglobin
IR: immediate-release
MEN 2: multiple endocrine neoplasia syndrome type 2
MTC: medullary thyroid carcinoma

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
metformin (Glucophage®, Glucophage® XR, Fortamet®*, Glumetza®*)	Regular-release (Glucophage): 500 mg PO BID or 850 mg PO QD; increase as needed in increments of 500 mg/week or 850 mg every 2 weeks Extended-release: • Fortamet, Glumetza: 1000 mg PO QD; increase as needed in increments of 500 mg/week • Glucophage XR: 500 mg PO QD; increase as needed in increments of 500 mg/week	Regular-release: 2550 mg/day Extended-release • Fortamet: 2500 mg/day • Glucophage XR, Glumetza: 2000 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Fortamet and Glumetza are non-formulary products.*

Appendix C: General Information

- The American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) and American Diabetes Association (ADA) state that because of its safety and efficacy, metformin is the cornerstone of monotherapy and is

usually the most appropriate initial choice for monotherapy unless there is a contraindication, such as renal disease, hepatic disease, gastrointestinal intolerance, or risk of lactic acidosis.

- The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) treatment algorithm on the approach to management of hyperglycemia in individuals with type 2 diabetes recommends lifestyle interventions (diet and exercise) plus metformin as the initial therapy. Patients not achieving goal are then recommended to receive other well-validated therapies such as basal insulin (considered rapidly effective) or a sulfonylurea (considered the least expensive) in combination with lifestyle interventions and metformin. When hypoglycemia is particularly undesirable, addition of less well-validated therapies, pioglitazone (a thiazolidinedione considered to have a low incidence of hypoglycemia) in addition to metformin or a GLP-1 agonist (if weight loss is a major consideration and the A1c level is close to target) in addition to metformin may be considered.
- The most recent glycemic goal recommended by ADA is an A1c level < 7% and the goal set by AACE is ≤ 6.5%, which is considered closer to normal.
- The recent clinical trials have aimed to reach A1c levels less than or equal to 6.5% with a variety of interventions. The results of the ACCORD study with the primary objective of decreasing cardiovascular disease (CVD) risk with interventions aimed at achieving an A1c level of < 6% vs. < 7.9%, showed excess CVD mortality in the intensive treatment group (2.6% vs. 1.8%, p=0.02) and more deaths from any cause than the standard-treatment group (5% vs. 4%, p=0.04). Results from ADVANCE and VADT studies did not demonstrate any excess total or CVD mortality with intensive regimens that achieved A1c levels comparable with the 6.5 % in ACCORD. None of the studies demonstrated a benefit of intensive glycemic control on the primary CVD outcomes. Clinical judgment based on the potential benefits and risk of reaching more stringent A1c goals should be applied for every patient. Factors such as life expectancy, risk of hypoglycemia, and the presence of CVD should be considered before intensifying the therapeutic regimen
- Bydureon, Ozempic, Tanzeum, Trulicity, and Victoza are contraindicated in patients with a personal or family history of MTC and MEN 2.
- Not approvable for appetite suppression or treatment of obesity since currently there are no studies to support the use of Byetta, Tanzeum, Trulicity, or Victoza for these conditions.
- Byetta and Victoza have not been studied sufficiently in patients with a history of pancreatitis. In clinical trials, there were 7 cases of pancreatitis among Victoza-treated patients and 1 case among comparator-treated patients. Byetta has been associated with acute pancreatitis in postmarketing data.
- Byetta has shown HbA1c reductions of 0.4 to 0.9% in clinical studies conducted in patients who have not achieved adequate glycemic control with sulfonylureas, metformin or combination of both. The mean baseline HbA1c levels ranged from 8.2 to 8.6%. Byetta added to a thiazolidinedione, with or without metformin, has shown 0.8% reduction in HbA1c. The mean baseline HbA1c was 7.9% for both groups. For patients with poorly controlled diabetes (e.g., HbA1c > 9%), insulin therapy may be a more appropriate therapeutic alternative.

- Victoza has shown a mean HbA1c reduction of 1% to 1.5% for the total populations in the trials in combination with metformin, sulfonylureas, combinations of both and with thiazolidinedione (LEAD-1 through LEAD-6). The mean baseline HbA1c for all LEAD studies was in a range from 8.2 to 8.5%. Victoza showed up to a 2.7% reduction in patients with inadequate glycemic control (mean baseline of 9.5% while failing metformin). Victoza's product labeling includes data showing superior blood glucose control and weight reduction when compared to Januvia® (sitagliptin). The label also includes approval to add basal insulin to Victoza in combination with metformin for adults with type 2 diabetes. Victoza's product labeling includes data showing superior blood glucose control and weight reduction when compared to Januvia (sitagliptin). The label also includes data to support the addition of Levemir (insulin detemir) to Victoza in combination with metformin for adults with type 2 diabetes. Victoza has not been studied in combination with prandial (mealtime) insulin.
- Trulicity has not been studied sufficiently in patients with a history of pancreatitis. In clinical trials, there was 1 reported case of chronic pancreatitis and 1 case of pancreatic cancer for Trulicity treated patients. Additionally, there were 3 reported cases of acute pancreatitis in the comparator-treated patients.
- Trulicity has shown a mean HbA1C reduction of 0.7% as monotherapy. The mean HbA1c reduction for total populations in the trials was 0.7 to 1.64% in combination with metformin, pioglitazone, combinations of both, or prandial insulin therapy (AWARD-1 through AWARD-6). The mean baseline for HbA1c for all AWARD studies was 7.6 to 8.1%. Trulicity showed up to a 1.6% reduction in HbA1c in combination with insulin lispro. Trulicity is the only GLP-1 receptor agonist studied in combination with prandial insulin therapy. The results of the trials showed superiority of Trulicity to reduce HbA1c from baseline when compared to Byetta (exenatide), Lantus (insulin glargine), and Januvia (sitagliptin). Trulicity 1.5 mg once weekly was non-inferior to Victoza (liraglutide) titrated to 1.8 mg once daily.

V. Dosage and Administration

Drug Name	Dosing Regimen	Maximum Dose
Adlyxin (lixisenatide)	Initial dose: 10 mcg SC daily for 14 days Maintenance dose: 20 mcg SC daily	20 mcg/day
Bydureon (exenatide ER)	2 mg SC once weekly	2 mg/week
Bydureon BCise (exenatide ER)	2 mg SC once weekly	2 mg/week
Byetta (exenatide IR)	5 mcg to 10 mcg SC twice daily	20 mcg/day
Ozempic (semaglutide)	0.25 mg to 1 mg SC once weekly	1 mg/week
Soliqua (lixisenatide/ insulin glargine)	15 units (15 units insulin/5 mcg lixisenatide) or 30 units (30 units insulin/10 mcg lixisenatide) SC QD	60 units (60 units insulin/20 mcg lixisenatide)/day
Tanzeum (liraglutide)	30 mg to 50 mg SC once weekly	50 mg/week
Trulicity (dulaglutide)	0.75 mg to 1.5 mg SC once weekly	1.5 mg/week
Victoza (liraglutide)	Initial: 0.6 mg SC daily for 7 days	1.8 mg/day

Drug Name	Dosing Regimen	Maximum Dose
	Maintenance: 1.2 mg to 1.8 mg SC daily	
Xultophy (liraglutide/ insulin degludec)	16 units (16 units insulin/0.58 mg liraglutide) SC QD	50 units (50 units insulin/1.8 mg liraglutide)/day

VI. Product Availability

Drug Name	Availability
Adlyxin (lixisenatide)	• Multi-dose prefilled pen: 50 mcg/mL in 3 mL (14 doses; 10 mcg/dose) • Multi-dose prefilled pen: 100 mcg/mL in 3 mL (14 doses; 20 mcg/dose)
Bydureon (exenatide ER)	• Single-dose tray: 2 mg vial • Single-dose prefilled pen: 2 mg pen
Bydureon BCise (exenatide ER)	Single-dose autoinjector: 2 mg
Byetta (exenatide IR)	• Prefilled pen: 5 mcg/dose (0.02 mL) in 1.2 mL (60 doses) • Prefilled pen: 10 mcg/dose (0.04 mL) in 2.4 mL (60 doses)
Ozempic (semaglutide)	• Prefilled pen: 2 mg/1.5mL (1.34 mg/mL) for 0.25 mg or 0.5 mg dose • Prefilled pen: 2 mg/1.5mL (1.34 mg/mL) for 1 mg dose
Soliqua (lixisenatide/ insulin glargine)	Single-patient use pen: 33 mcg/100 units per mL in 3 mL
Tanzeum (liraglutide)	Single dose prefilled pen powder: 30 mg and 50 mg
Trulicity (dulaglutide)	• Single-dose prefilled pen: 0.75 mg/0.5mL and 1.5 mg/0.5mL • Single-dose prefilled syringe: 0.75 mg/0.5mL and 1.5 mg/0.5mL
Victoza (liraglutide)	Multi-dose prefilled pen: 6 mg/mL in 3 mL (doses of 0.6 mg, 1.2 mg, or 1.8 mg)
Xultophy (liraglutide/ insulin degludec)	Single-patient use pen: 3.6 mg/100 units per mL in 3 mL

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Converted to new template; minor changes to verbiage and grammar. References updated.	01.17	08.17
Added Xultophy to criteria.	07.14	08.17
Added: "For Adlyxin, Bydureon, Byetta, Soliqua, Tanzeum, and Xultophy: Failure of Victoza and Trulicity unless both are contraindicated or clinically significant adverse effects are experienced"	08.21.17	11.17
1Q18 annual review: Removed requirement for documentation of baseline A1c as this does not dictate coverage decision; Added option for members with A1c ≥ 9% to bypass previous use of metformin for 3 months per ADA guidelines (concurrent metformin use is still required); Removed requirement for concurrent use of metformin on re-auth; References reviewed and updated.	11.30.17	02.18
Added Ozempic to criteria.	03.22.18	05.18
No signifcant changes: removed redirection to Victoza and Trulicity for Ozempic per SDC	08.01.18	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical

practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions. Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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