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

Reference Number: CP.CPA.16
Effective Date: 11.16.16
Last Review Date: 02.20
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 contain a synthetic glucagon-like peptide-1 (GLP-1) receptor agonist and require prior authorization: dulaglutide (Trulicity®), exenatide ER (Bydureon®), exenatide IR (Byetta®), liraglutide (Victoza®), liraglutide/insulin degludec (Xultophy®), lixisenatide (Adlyxin®), lixisenatide/insulin glargine (Soliqua®), and semaglutide (Ozempic®, Rybelsus®).

FDA Approved Indication(s)

GLP-1 receptor agonists are indicated as adjunct to diet and exercise to improve glycemic control with type 2 diabetes mellitus. Victoza is indicated in patients 10 years of age and older, while the other GLP-1 receptor agonists are indicated in adults

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

Limitation(s) of use:

- Trulicity, Bydureon, Bydureon BCise, Xultophy, and Rybelsus 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.
- Trulicity is 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.
- Bydureon and Bydureon BCise are extended-release formulations of exenatide. Do not coadminister with other exenatide containing products.

Policy/Criteria

Provider must submit documentation (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. Age is one of the following (a or b):
   a. Victoza: ≥ 10 years;
   b. All other GLP-1 receptor agonists: ≥ 18 years;
3. Member meets one of the following (a or b):
   a. Failure of ≥ 3 consecutive months of metformin as evidenced by HbA1c ≥ 7%, unless contraindicated or clinically significant adverse effects are experienced;
   b. HbA1c drawn within the past 3 months is ≥ 8.5%, and concurrent use of metformin unless contraindicated or clinically significant adverse effects are experienced;
4. For Adlyxin, Bydureon, Byetta, Soliqua, Tanzeum, and Xultophy: Failure of Victoza and Trulicity, unless clinically significant adverse effects are experienced or both are contraindicated;
5. For Rybelsus: Failure of a sodium-glucose co-transporter 2 (SGLT2) inhibitor (see *Appendix B*), unless clinically significant adverse effects are experienced or all are contraindicated;
6. Dose does not exceed one of the following:
   a. Adlyxin: 20 mcg per day (2 pens per month);
   b. Bydureon: 2 mg per week (4 vials or pens per month);
   c. Byetta: 20 mcg per day (4 vials or pens per month);
   d. Ozempic: 1 mg per week (2 pens per month);
   e. Rybelsus: 14 mg per day (1 tablet per day);
   f. Soliqua: 60 units/20 mcg per day (6 pens per month);
   g. Trulicity: 1.5 mg per week (4 vials or pens per month);
   h. Victoza: 1.8 mg per day (4 vials or pens per month);
   i. Xultophy: 50 units/1.8 mg per day (6 pens per month).

Approval duration:
Rybelsus – 12 months
All other agents – 6 months or member's renewal period, whichever is longer

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial.

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 one of the following:
   a. Adlyxin: 20 mcg per day (2 pens per month);
   b. Bydureon: 2 mg per week (4 vials or pens per month);
   c. Byetta: 20 mcg per day (4 vials or pens per month);

d. Ozempic: 1 mg per week (2 pens per month);
e. Rybelsus: 14 mg per day (1 tablet per day);
f. Soliqua: 60 units/20 mcg per day (6 pens per month);
g. Trulicity: 1.5 mg per week (4 vials or pens per month);
h. Victoza: 1.8 mg per day (4 vials or pens per month);
i. Xultophy: 50 units/1.8 mg per day (6 pens per month).

Approval duration:
Rybelsus – 12 months
All other agents – 6 months or member's renewal period, whichever is longer

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 the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial.

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.

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
SGLT2: sodium-glucose co-transporter 2

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	Regular-release: 2,550 mg/day Extended-release: 2,000 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Extended-release: • Fortamet, Glumetza: 1,000 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	
SGLT2 Inhibitors		
Farxiga® (dapagliflozin)	5 mg PO QD To reduce the risk of hospitalization for heart failure, the recommended dose is 10 mg PO QD	10 mg/day
Glyxambi® (empagliflozin/linagliptin)	One 10/5 mg tablet PO QD	25/5 mg/day
Invokamet® (canagliflozin/metformin)	One 50/500 mg tablet PO BID	300/2,000 mg/day
Invokamet® XR (canagliflozin/metformin)	Two 50/500 mg tablets PO QD	300/2,000 mg/day
Invokana® (canagliflozin)	100 mg PO QD	300 mg/day
Jardiance® (empagliflozin)	10 mg PO QD	25 mg/day
Qtern® (dapagliflozin/saxagliptin)	One 5/5 mg tablet PO QD	10/5 mg/day
Qternmet® XR (dapagliflozin/saxagliptin/metformin)	Individualized dose PO QD	10/5/2,000 mg/day
Steglujan™ (ertugliflozin/sitagliptin)	One 5/100 mg tablet PO QD	15/100 mg/day
Synjardy® (empagliflozin/metformin)	Individualized dose PO BID	25/2,000 mg/day
Synjardy® XR (empagliflozin/metformin)	Individualized dose PO QD	25/2,000 mg/day
Trijardy™ XR (empagliflozin/linagliptin/ metformin)	Individualized dose PO QD	25/5/2,000 mg/day
Xigduo® XR (dapagliflozin/metformin)	Individualized dose PO QD	10/2,000 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: Contraindications/Boxed Warnings

- Contraindication(s):

- Hypersensitivity to any product components
- Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 (*all GLP-1 receptor agonists other than Byetta, Adlyxin, and Soliqua*)
- Use during episodes of hypoglycemia (*Soliqua and Xultophy only*)

- Boxed warning(s): thyroid C-cell tumors (*all GLP-1 receptor agonists other than Byetta, Adlyxin, and Soliqua*)

Appendix D: General Information

- A double-blind, placebo-controlled dose-response trial by Garber et al. found the maximal efficacy of metformin to occur at doses of 2,000 mg. However, the difference in adjusted mean change in HbA1c between the 1,500 and 2,000 mg doses was 0.3%, suggesting that the improvement in glycemic control provided by the additional 500 mg may be insufficient when HbA1c is > 7%.
- Per the 2019 American Diabetes Association (ADA) and 2019 American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) guidelines:
  - Metformin is recommended for all patients with type 2 diabetes. Monotherapy is recommended for most patients; however:
    - Starting with dual therapy (i.e., metformin plus another agent, such as a sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 inhibitor, sodium-glucose co-transporter inhibitor, GLP-1 receptor agonist, or basal insulin) may be considered for patients with baseline HbA1c ≥ 1.5% above their target per the ADA (≥ 7.5% per the AACE/ACE). According to the ADA, a reasonable HbA1c target for many non-pregnant adults is < 7% (≤ 6.5% per the AACE/ACE).
    - Starting with combination injectable therapy (i.e., with GLP-1 receptor agonist or insulin) may be considered for patients with baseline HbA1c ≥ 10% or ≥ 2% above their target per the ADA (> 9% if symptoms are present per the AACE/ACE).
  - If the target HbA1c is not achieved after approximately 3 months of monotherapy, dual therapy should be initiated. If dual therapy is inadequate after 3 months, triple therapy should be initiated. Finally, if triple therapy fails to bring a patient to goal, combination injectable therapy should be initiated. Each non-insulin agent added to initial therapy can lower HbA1c by 0.7-1%.
- 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 QD for 14 days Maintenance dose: 20 mcg SC QD	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 BID	20 mcg/day
Ozempic (semaglutide)	0.25 mg to 1 mg SC once weekly	1 mg/week
Rybelsus (semaglutide)	Initial dose: 3 mg PO QD. After 30 days on the 3 mg dose, increase to 7 mg PO QD. May increase to 14 mg PO QD if needed after at least 30 days on the 7 mg dose	14 mg/day

Drug Name	Dosing Regimen	Maximum Dose
Soliqua (lixisenatide/ insulin glargine)	Treatment naïve to basal insulin or GLP-1 receptor agonist, currently on a GLP-1 receptor agonist, or currently on less than 30 units of basal insulin daily: 15 units (15 units insulin/5 mcg lixisenatide) SC QD Currently on 30 to 60 units of basal insulin daily, with or without GLP-1 receptor agonist: 30 units (30 units insulin/10 mcg lixisenatide) SC QD	60 units insulin/20 mcg lixisenatide/day
Trulicity (dulaglutide)	0.75 mg to 1.5 mg SC once weekly	1.5 mg/week
Victoza (liraglutide)	Initial: 0.6 mg SC QD for 7 days Maintenance: 1.2 mg to 1.8 mg SC QD	1.8 mg/day
Xultophy (liraglutide/ insulin degludec)	Treatment naïve to basal insulin or GLP-1 receptor agonist: 10 units (10 units of insulin/0.36 mg liraglutide) SC QD Treatment experienced to basal insulin or GLP-1 receptor agonist: 16 units (16 units insulin/0.58 mg liraglutide) SC QD	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), 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), 10 mcg/dose (0.04 mL) in 2.4 mL (60 doses)
Ozempic (semaglutide)	Prefilled pen: 2 mg/1.5 mL (1.34 mg/mL) for 0.25 mg or 0.5 mg dose; 2 mg/1.5 mL (1.34 mg/mL) for 1 mg dose
Rybelsus (semaglutide)	Tablet: 3 mg, 7 mg, 14 mg
Soliqua (lixisenatide/ insulin glargine)	Single-patient use pen: 33 mcg/100 units per mL in 3 mL
Trulicity (dulaglutide)	Single-dose prefilled pen: 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

VII. References

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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 significant changes: removed redirection to Victoza and Trulicity for Ozempic per SDC	08.01.18	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2019 annual review: added age ≥ 18 years; clarified metformin trial required to be consecutive months; modified minimum A1c related for concurrent use of metformin from 9% to 8.5% based on 2019 ADA guidelines; removed medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 exclusions from Section III; removed Tanzeum as GlaxoSmithKline discontinued its manufacturing/sale in July 2018; initial approval duration modified to length of benefit; references reviewed and updated.	10.12.18	02.19
No significant changes; updated FDA approved indications for Soliqua and Xultophy to remove requirement for failure of basal insulin and corresponding GLP-1 receptor agonists, lixisenatide and liraglutide respectively; updated dosage and administration for treatment naïve patients; references reviewed and updated.	03.12.19	
Clarified that failure of metformin must be evidenced by HbA1c at least 7%.	04.22.19	05.19
RT4: updated criteria to reflect Victoza's pediatric expansion to ages 10 and older.	06.25.19	
Revised approval durations from length of benefit to 12 months.	10.16.19	
Added new oral semaglutide formulation, Rybelsus; references reviewed and updated.	10.17.19	11.19
Revised approval durations for injectable agents from 12 months to "6 months or member's renewal period, whichever is longer."	11.22.19	
1Q 2020 annual review: no significant changes; references reviewed and updated.	11.23.19	02.20
For Rybelsus requests, added requirement for trial of a SGLT2 inhibitor per SDC and prior clinical guidance; RT4: added new Ozempic cardiovasular risk reduction indication; removed first-line therapy limitation of use for Ozempic, Victoza, Byetta, Soliqua, and Adlyxin.	03.05.20	

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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