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

Reference Number: AZ.CP.PMN.183
Effective Date: 11.16.16
Last Review Date: 04.21
Line of Business: Arizona Medicaid (AzCH-CCP and Care1st)

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®, Bydureon® BCise™), exenatide IR (Byetta®), liraglutide (Victoza®), liraglutide/insulin degludec (Xultophy®), lixisenatide (Adlyxin®), lixisenatide/insulin glargine (Soliqua®), and semaglutide (Ozempic®, Rybelsus®).

AHCCCS preferred drugs in this class include Bydureon (exenatide extended-release) pens, Byetta (exenatide), Trulicity (dulaglutide), and Victoza (liraglutide).

AHCCCS non-preferred drugs in this class include Adlyxin (lixisenatide), Bydureon BCise (exenatide extended-release), Soliqua (lixisenatide/insulin glargine), Xultophy (liraglutide/insulin degludec), and semaglutide (Ozempic®, Rybelsus®).

FDA approved indications

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, Trulicity, 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 (*Ozempic, Trulicity, Victoza*);
- Cardiovascular risk factors (*Trulicity only*).

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 (which may include office chart notes and lab results) supporting that member has met all approval criteria

It is the policy of Arizona Complete Health-Complete Care Plan and Care1st 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 at a minimum daily dose of 1500mg 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 at a minimum daily dose of 1500mg, unless contraindicated or clinically significant adverse effects are experienced;
4. Request meets one of the following (a, b, c, d, or e):
   a. Request is for Bydureon pens, Byetta, Trulicity, or Victoza;
   b. Request is for Ozempic: member has established cardiovascular disease (e.g., ASCVD), and Victoza and Trulicity are contraindicated or clinically significant adverse effects are experienced;
   c. Request is for Adlyxin, Bydureon BCise, Soliqua, Xultophy, or Ozempic (without established cardiovascular disease): failure of ≥ 3 consecutive months of Bydureon pens/Byetta, Trulicity, and Victoza, unless contraindicated or clinically significant adverse effects are experienced;
   d. Request is for Victoza 1.8mg per day (3 Pen Pack): failure to achieve HbA1c of 7% with Victoza 1.2mg per day (2 pen pack);
   e. Request is for Rybelsus: failure of a sodium-glucose co-transporter 2 (SGLT2) inhibitor (*see Appendix B*), Bydureon pens/Byetta, Trulicity, and Victoza, unless clinically significant adverse effects are experienced or all are contraindicated;
5. Dose does not exceed the FDA approved maximum recommended dose for the relevant indication.

Approval duration: 12 months

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): AZ.CP.PMN.53 for Arizona Medicaid.

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. Request meets one of the following (a, b, c, d, or e):
   a. Request is for Bydureon pens, Byetta, Trulicity, or Victoza;
   b. Request is for Ozempic: member has established cardiovascular disease (e.g., ASCVD), and Victoza and Trulicity are contraindicated or clinically significant adverse effects are experienced;
   c. Request is for Adlyxin, Bydureon BCise, Soliqua, Xultophy, or Ozempic (without established cardiovascular disease): failure of ≥ 3 consecutive months of Bydureon pens/Byetta, Trulicity, and Victoza, unless contraindicated or clinically significant adverse effects are experienced;
   d. Request is for Victoza 1.8mg per day (3 Pen Pack): failure to achieve HbA1c of 7% with Victoza 1.2mg per day (2 pen pack);
   e. Request is for Rybelsus: failure of a sodium-glucose co-transporter 2 (SGLT2) inhibitor (*see Appendix B*), Bydureon pens/Byetta, Trulicity, and Victoza, unless clinically significant adverse effects are experienced or all are contraindicated;
3. Member is responding positively to therapy;
4. Documentation of continued metformin therapy (unless contraindicated);
5. If request is for a dose increase, request meets one of the following (a or b):
   a. Trulicity (i or ii):
      i. If request is for dose increase from 1.5 mg, new dose does not exceed 3 mg per week (4 vials or pens per month);
      ii. If request is for dose increase from 3 mg, new dose does not exceed 4.5 mg per week (4 vials or pens per month);
   b. All other GLP-1 receptor agonists: New dose does not exceed the FDA-approved maximum recommended dose (*see Section V*).

Approval duration: 12 months

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): AZ.CP.PMN.53 for Arizona Medicaid.

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 – AZ.CP.PMN.53 for Medicaid 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
ASCVD: atherosclerotic cardiovascular disease
ER: extended-release
DM: diabetes mellitus
FDA: Food and Drug Administration
GLP-1: glucagon-like peptide type 1
HbA1c: glycated hemoglobin
IR: immediate-release
SC: subcutaneous

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 for all relevant lines of business and may require prior authorization.

Drug	Dosing Regimen	Dose Limit/ Maximum Dose
metformin (Fortamet®, Glucophage®, Glucophage® XR, 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: 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	Regular-release: 2,550 mg/day Extended-release: 2,000 mg/day
SGLT2 Inhibitors		
Farxiga® (dapagliflozin)	5 mg PO QD To reduce the risk of hospitalization for heart failure,	10 mg/day

Drug	Dosing Regimen	Dose Limit/ Maximum Dose
	the recommended dose is 10 mg PO QD	
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.

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 Adlyxin, and Soliqua*)
  - Use during episodes of hypoglycemia (*Soliqua and Xultophy only*)
  - History of drug-induced immune-mediated thrombocytopenia from exenatide products (*Bydureon, Bydureon BCise, and Byetta 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 2020 American Diabetes Association (ADA) and 2020 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 therapy with insulin may be considered for patients with baseline HbA1c > 10% 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%.
- Although Trulicity is currently the only GLP-1 receptor agonist that is FDA approved for use in patients with multiple cardiovascular risk factors, the 2020 ADA guidelines recognize Ozempic, Trulicity, and Victoza as agents that confer cardiovascular benefit and recommend the use of any of the three in patients at high risk of ASCVD, without preference for any one over the other. In addition, patients with multiple cardiovascular risk factors were included in each drug's cardiovascular outcomes trial.
- Examples of cardiovascular risk factors may include but are not limited to: dyslipidemia, hypertension, obesity, a family history of premature coronary disease, smoking, chronic kidney disease, and presence of albuminuria.

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
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. May increase to 3 mg once weekly if needed after at least 4 weeks on 1.5 mg dose. May further increase to 4.5 mg once weekly if needed after at least 4 weeks on 3 mg dose.	4.5 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	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/1.5mL (1.34 mg/mL) for 0.25 mg or 0.5 mg dose; 2 mg/1.5mL (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/0.5 mL, 1.5 mg/0.5 mL, 3 mg/0.5 mL, 4.5 mg/0.5 mL
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
Policy Created	05.03.17	11.17
Added information related to Tanzeum market withdrawal. Requests should be discussed with the provider to ensure they are aware of the product discontinuation.	11.20.17	
Annual Review – Added reference to 2018 ADA treatment guidelines. Modified approval guidelines to allow for initial therapy in combination with metformin for patients with baseline A1c over 9% per ADA guidelines. Added new Victoza indication for prevention of adverse cardiovascular events.	09.12.18	
Removed Tanzeum as it was withdrawn from the market; Added AHCCCS non-preferred drugs; edited limitations of use based on CP.PMN.183; added metformin minimum daily doses; modified minimum A1c related for concurrent use of metformin from 9% to 8.5% based on 2019 ADA guidelines; Added requirement for a non-Preferred GLP-1 agonist: failure of ≥ 3 consecutive months of all preferred GLP-1 agonist, unless contraindicated or clinically significant adverse effects are experienced; Added requirement for Victoza 3 Pen Pack: failure to achieve HbA1c of 7% with Victoza 1.2 mg per day (2 pen pack); removed requirement for switching to insulin therapy or referral to an endocrinologist in case of	03.22.19	4.19

Reviews, Revisions, and Approvals	Date	P&T Approval Date
inadequate response to therapy; switched appendix orders to match with CP.PMN.183		
Changed reference from CP.PMN.183 to AZ.CP.PMN.53- policy change due to renumeration and edits. Minor formatting edits.	8.8.19	
Added criterion for history of failure of preferred GLP-1 agonists for Continued Therapy; Added dosing regimen to Appendix B: Bydureon, Byetta, and Victoza.	10.07.19	10.19
Q1 2020 annual review; Policy number updated from AZ.CP.PMN.42 to AZ.CP.PMN.183 to align with corporate criteria; Added information for Rybelsus; Updated references.	01.2020	01.2020
Updated "FDA Approved Indications" section to include Trulicity's new FDA indication: cardiovascular risk reduction in patients with established cardiovascular disease or with multiple cardiovascular risk factors; added new Ozempic cardiovasular risk reduction indication; updated criteria to reflect Victoza's pediatric expansion to ages 10 and older; modified criteria to allow Trulicity or Ozempic in patients with established cardiovascular disease or multiple cardiovascular risk factors if contraindicated to the preferred agent Victoza; removed Criterion B of Section III. Diagnoses/Indications for which coverage is NOT authorized All GLP-1 receptor agonists: Patients with a personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2); added new exenatide contraindication to Appendix C; references reviewed and updated.	07.20.20	08.20
RT4: added new dosage strength (3 mg, 4.5 mg) forms for Trulicity	09.29.20	
1Q 2021 annual review: no significant changes; added new dosage strength (4 mg/3 mL) form for Ozempic; references reviewed and updated.	10.26.20	02.21
AHCCCS preferred Hypoglycemics, Incretin Mimetics update effective 4/1/21: Trulicity moved from non-preferred to preferred; Ozempic requests for member who have established cardiovascular disease (e.g., ASCVD) require failure of Victoza and Trulicity unless	03.17.21	04.21

Reviews, Revisions, and Approvals	Date	P&T Approval Date
contraindicated or clinically significant adverse effects are experienced; Non-preferred GLP-1 agonists containing therapy such as Adlyxin, Bydureon BCise, Soliqua, Xultophy, and Ozempic (without established cardiovascular disease) require failure of ≥ 3 consecutive months of Bydureon pens/Byetta, Trulicity, and Victoza, unless contraindicated or clinically significant adverse effects are experienced; Rybelsus requests require failure of a sodium-glucose co-transporter 2 (SGLT2) inhibitor (see Appendix B), Bydureon pens/Byetta, Trulicity, and Victoza, unless clinically significant adverse effects are experienced or all are contraindicated; Initial approval duration changed from 6 months to 12 months.		
Added Care1st logo. Added verbiage to specify that criteria also applies to Care1st.	5.10.21	04.21

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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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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