

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

Reference Number: HIM.PA.53

Effective Date: 03.01.18

Last Review Date: 05.19

Line of Business: HIM

[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 IR (Byetta[®]), liraglutide (Victoza[®]), and liraglutide/insulin degludec (Xultophy[®]).

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.

Victoza is 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:

- GLP-1 receptor agonists are not recommended as a first-line therapy for patients inadequately controlled on diet and exercise.
- Other than Xultophy which contains 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.

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 $\geq 7\%$, unless contraindicated or clinically significant adverse effects are experienced;
 - b. HbA1c drawn within the past 3 months is $\geq 8.5\%$, and concurrent use of metformin unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed the FDA-approved maximum recommended dose (*see Section V*).

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): HIM.PHAR.21 for health insurance marketplace.

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 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): HIM.PHAR.21 for health insurance marketplace.

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 policies – HIM.PHAR.21 for health insurance marketplace 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

ER: extended-release

FDA: Food and Drug Administration

GLP-1: glucagon-like peptide-1

HbA1c: glycated hemoglobin

IR: immediate-release

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 Name | 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: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> Fortamet: 2,500 mg/day Glucophage XR, Glumetza: 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 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 2017 American Association of Clinical Endocrinologists and American College of Endocrinology (AAACE/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 \geq 1.5% above their target per the

ADA ($\geq 7.5\%$ per the AACE/ACE). According to the ADA, a reasonable HbA1c target for many non-pregnant adults is $< 7\%$.

- Starting with combination injectable therapy (i.e., with GLP-1 receptor agonist or insulin) may be considered for patients with baseline HbA1c $\geq 10\%$ or $\geq 2\%$ above their target per the ADA ($\geq 9\%$ 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%.

V. Dosage and Administration

| Drug Name | Dosing Regimen | Maximum Dose |
|---|---|---|
| Byetta (exenatide IR) | 5 mcg to 10 mcg SC BID | 20 mcg/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 |
|---|--|
| 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) |
| 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

1. American Diabetes Association. Standards of medical care in diabetes—2019. Diabetes Care. 2019; 42(suppl 1): S1-S193.
2. Byetta Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals, LP; December 2018. Available at: www.byetta.com. Accessed June 25, 2019.
3. Trulicity Prescribing Information. Indianapolis, IN: Eli Lilly and Company, Inc; January 2019. Available at: www.trulicity.com. Accessed June 25, 2019.

4. Victoza Prescribing Information. Princeton, NJ: Novo Nordisk Inc; June 2019. Available at: www.victoza.com. Accessed June 25, 2019.
5. Garber AJ, Duncan TG, Goodman AM, et al. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med.* 1997; 102: 491-497.
6. Garber AJ, Abrahamson MJ, Barzilay, JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2017 executive summary. *Endocr Pract.* 2017; 23(2): 207-238.
7. Xultophy Prescribing Information. Bagsvaerd, Denmark: Novo Nordisk A/S; February 2019. Available at: www.xultophy.com. Accessed June 25, 2019.

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|--|----------|-------------------|
| Changed guideline to new format. Extended approval period from 6 months to 12 months. | 08.16 | 08.16 |
| Removed age restriction. Modified A1c requirement from > 7% to > 6.5% and specified time frame for lab. Added specific dose and duration for metformin trial. Clarified criterion for failure of other anti-diabetic agents to specifically require a sulfonylurea and pioglitazone be used concurrently with metformin for 3 consecutive months. Removed criterion regarding concurrent insulin use as it is not an absolute contraindication. Modified initial approval duration from 12 months to 6 months to allow for earlier assessment of therapeutic response. Added criteria surrounding required therapeutic response for re-auth. | 04.17 | 08.17 |
| Added age restriction as safety and efficacy have not been established in pediatric populations. Removed requirement that metformin must have been used with a sulfonylurea and pioglitazone as GLP-1 agonists are similar place of therapy as these agents, and the guidelines do not prefer one over the other. | 08.18.17 | 11.17 |
| Removed requirement for diagnosis Removed requirement for A1C submission Changed requirement for Metformin trial to be for 3 months without mandating a specific dose Allow first line use for members with A1C >= 9% References reviewed and updated | 11.17 | 02.18 |
| 1Q 2019 annual review: clarified that all GLP-1 receptor agonists require PA (rather than ST) and added diagnosis per SDC; added Xultophy; removed Tanzeum as GlaxoSmithKline discontinued its manufacturing/sale in July 2018; modified minimum A1c related | 09.19.18 | 02.19 |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|----------|-------------------|
| for concurrent use of metformin from 9% to 8.5% based on 2019 ADA guidelines; references reviewed and updated. | | |
| No significant changes; updated FDA approved indication for Xultophy to remove requirement for failure of basal insulin and liraglutide; 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 | |

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

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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 Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the non-formulary policy; HIM.PA.103.

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