Clinical Policy: GLP-1 Receptor Agonists

Reference Number: AZ.CP.PHAR.42
Effective Date: 11.16.16
Last Review Date: 09.12.18
Line of Business: Arizona Medicaid

Revision Log

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

Description

Glucagon-Like-Peptide-1 Analogs activate the GLP-1 receptor to increase insulin release in the presence of elevated glucose concentrations, facilitate the reduction of glucagon release and cause a delay in gastric emptying.

The following are GLP-1 Analogs requiring prior authorization;
AHCS Preferred Agents: Bydureon® (exenatide extended release), Byetta (exenatide), Victoza® (liraglutide)

Non Preferred Agents: Adlyxin® (lixisenatide), Soliqua® (glargine-lixisenatide), Tanzeum® (albiglutide), Trulicity® (dulaglutide) and Bydureon BCise® (exenatide extended release auto-injector)

FDA approved indications

Adlyxin, Bydureon, Byetta, Tanzeum, Trulicity, Victoza: An 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 mellitis and established cardiovascular disease.

Soliqua: An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 60 units daily) or lixisenatide.

Limitation of use: GLP-1 Analogs are not recommended for use as first-line therapy in patients inadequately controlled on diet and exercise.

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 health plans affiliated with Centene Corporation® that Adlyxin, Bydureon, Byetta, Soliqua, Tanzeum, Trulicity, and Victoza are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Diagnosis of Type 2 Diabetes;
2. Documentation of baseline HbA1c level greater than 6.5;
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, unless contraindicated or clinically significant adverse effects are experienced;
4. HbA1c drawn within the past 3 months is ≥ 9%, and concurrent use of metformin unless contraindicated or clinically significant adverse effects are experienced;For authorization of **non-preferred agents (Adlyxin, Tanzeum*, Trulicity, Soliqua, Bydureon BCise)**, failure or documented clinically significant adverse effects to ALL preferred formulary agents;
5. Dose does not exceed the FDA approved maximum recommended dose for the relevant indication.

Initial Approval duration: 6 months

**Tanzeum is being discontinued. Requests should be discussed with the provider to ensure the provider is aware this product will be removed from the market.*

B. Other diagnoses/indications

1. Refer to CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized)

II. Continued Therapy

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

1. Currently receiving medication via a health plan affiliated with Centene Corporation or member has previously met initial approval criteria;
2. Documentation of positive response to therapy (i.e. >0.5% reduction in HbA1c) at the end of initial authorization period is required. If inadequate response to therapy, either a switch to insulin therapy, addition of insulin(s) to GLP-1 receptor agonist, or a referral to an endocrinologist will be required;
3. Documentation of continued metformin therapy (unless contraindicated);
4. If request is for a dose increase, new dose does not FDA approved maximum recommended dose for the relevant indication.

Approval duration: 12 months*

**Tanzeum is being discontinued. Requests should be discussed with the provider to ensure the provider is aware this product will be removed from the market.*

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

1. Currently receiving medication via a health plan affiliated with Centene Corporation and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to CP. PMN.53if 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. PMN.53or evidence of coverage documents
B. Bydureon, Victoza, Tanzeum, Trulicity: Patients with a personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2)

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
DM: diabetes mellitus
GLP-1: glucagon like peptide type 1
HbA1C: glycated hemoglobin
SC: subcutaneous

Appendix B: General Information

- GlaxoSmithKline (GSK), manufacturer of Tanzeum, is discontinuing the commercial sale of Tanzeum (30 mg and 50 mg in a single-dose pen for injection). It is expected that the commercial supply will be depleted by July 2018. Providers should initiate discussions with patients currently on Tanzeum with a plan to transition all patients to an alternative therapy as appropriate by July 2018. Tanzeum should not be initiated in new patients.
- 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 HbA1c level is close to target) in addition to metformin may be considered.
- The most recent glycemic goal recommended by ADA is an HbA1c 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 HbA1c 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 CVD risk with interventions aimed at achieving an HbA1c 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 HbA1c 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 HbA1c 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, Tanzeum, Trulicity and Victoza are contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) and Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- Not approvable for appetite suppression or treatment of obesity since currently there are no studies to support the use of Adlyxin, Bydureon, Byetta, Soliqua, 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 post-marketing 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, and 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.

Appendix C: Therapeutic Alternatives

Drug	Dosing Regimen	Dose Limit/ Maximum Dose
metformin (Glucophage®)	500 mg BID or 850 mg PO QD, titrate up to 2,550 mg/day	2,550 mg/day
metformin ER (Glucophage® XR)	500 mg PO QD, increase up to 2,000 mg/day	2,000 mg/day
glyburide/metformin (Glucovance®)	1.25/250 mg PO QD, up to 20/2,000 mg/day	20/2,000 mg/day
glipizide/metformin (Metaglip™)	Initial therapy:2.5/250 mg PO QD to 10/1,000 mg or 10/2,000 mg in divided doses Second-line therapy (patients not adequately controlled on glipizide or metformin): 2.5/500 mg or 5/500 PO BID to 20/2,000 mg/day	Initial therapy: 10/1,000 mg/day or 10/2,000 mg/day Second-line therapy: 20/2,000 mg/day
glyburide (Micronase®, Diabeta®)	2.5-5 mg PO QD, up to 20 mg/day	20 mg/day
glyburide, micronized (Glynase® Pres Tab)	1.5 to 3 mg PO QD, up to 12 mg/day	12 mg/day
glimepiride (Amaryl®)	1-2 mg PO QD, up to 8 mg/day	8 mg/day
glipizide (Glucotrol®)	5-40 mg PO QD	40 mg/day
glipizide ER (Glucotrol XL®)	5-20 mg PO QD	20 mg/day
pioglitazone (Actos®)	15-45 mg PO QD	45 mg/day
pioglitazone/metformin (ACTOplus Met®))	15 mg/500 mg PO QD, up to 45 mg/2,550 mg/day	45 mg/2,550 mg/day
pioglitazone/glimepiride (Duetact®)	30 mg/2 mg PO QD, up to 45 mg/8 mg PO per day	45 mg/8 mg
Januvia® (sitagliptin)	25 mg to 100 mg PO QD	100 mg/day
Janumet® (sitagliptin/metformin)	50 mg/500 mg, 50 mg/1,000 mg PO BID	100 mg sitagliptin and 2,000 mg metformin
Janumet-XR® (sitagliptin/metformin extended release)	50 mg/500 mg, 50 mg/1,000 mg, 100 mg/1,000 mg PO QD	100 mg sitagliptin and 2,000 mg metformin
Onglyza® (saxagliptin)	2.5 mg to 5 mg PO QD	5 mg/day
Kombiglyze-XR® (saxagliptin/metformin extended release)	5 mg/500 mg, 2.5 mg/1,000 mg, 5 mg/1,000 mg PO QD	5 mg saxagliptin and 2,000 mg metformin

Drug	Dosing Regimen	Dose Limit/ Maximum Dose
Tradjenta® (linagliptin)	5 mg PO QD	5 mg/day
Jentadueto® (linagliptin/metformin)	2.5 mg/500 mg, 2.5 mg/850 mg, 2.5 mg/1,000 mg PO BID	5 mg linagliptin and 2,000 mg metformin
Humulin® N (NPH human isophane)	0.5 to 1 U/kg SC QD	Individualize dosage
Lantus® (insulin glargine)	DM Type 2 (Insulin naïve): Start at 10 U SC QD, maintenance dose ranges from 2-100 U/day. Switching from once-daily NPH: Same total daily dosing Switching from twice-daily NPH: Reduce Lantus dose by 20% at initiation	Individualize dosage
Levemir® (insulin detemir)	Insulin-naïve patients with Type 2 diabetes: Start at 0.1 to 0.2 U/ kg SC QD in the evening or 10 units SC QD or BID, and the dose adjusted to achieve glycemic targets Patients with type 1 or 2 currently receiving only basal insulin or basal-bolus: Switch can be done on a unit-to-unit basis for changing the basal insulin to Levemir.	Individualize dosage

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.

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
lixisenatide (Adlyxin) Non Preferred Drug	Type 2 DM	Initial dose: 10 mcg SC daily for 14 days Maintenance dose: 20 mcg SC daily	20 mcg SC per day
exenatide extended release suspension (Bydureon) **Preferred Drug**	Type 2 DM	2mg SC once weekly	2mg SC per week
exenatide (Byetta) **Preferred Drug**	Type 2 DM	Initiate at 5 mcg SC BID at any time within the 60 minute period before	20mcg SC per day

		morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart). Based on clinical response, increase the dose to 10 mcg SC BID after 1 month.	
lixisenatide-insulin glargine (Soliqua) Non Preferred Drug	Type 2 DM	Discontinue therapy with lixisenatide or basal insulin prior to initiation of Soliqua. In patients inadequately controlled on <30 units of basal insulin or on lixisenatide, the starting dosage is 15 units insulin glargine/5 mcg lixisenatide SC QD In patients inadequately controlled on 30 to 60 units of basal insulin, the starting dosage is 30 units insulin glargine/10 mcg lixisenatide given subcutaneously once daily	Maximum daily dosage is 60 units of insulin glargine and 20 mcg of lixisenatide.
albiglutide (Tanzeum) Non Preferred Drug	Type 2 DM	30-50mg SC once weekly	50mg SC once weekly
dulaglutide (Trulicity) Non Preferred Drug	Type 2 DM	Initial dose of 0.75 mg SC once weekly, up to 1.5 mg SC once weekly for additional glycemic control	1.5mg SC once weekly
liraglutide (Victoza)	Type 2 DM	Initiate at 0.6 mg SC QD for 1 week. After	1.8mg SC once daily

Preferred Drug		one week at 0.6 mg QD, increase dose to 1.2 mg SC QD. If 1.2 mg QD does not result in acceptable glycemic control, dose may increase to 1.8 mg SC QD.	

VI. Product Availability

Drug	Availability
lixisenatide (Adlyxin)	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 (for 14 doses; 20mcg/dose)
exenatide extended release suspension (Bydureon)	Single-dose tray: 2 mg vial; Single-dose Pre-filled Pen: 2 mg pen
exenatide (Byetta)	Pre-filled Pen: 5 mcg/dose (0.02 ml), 60 doses, 1.2 ml pre-filled pen; 10 mcg/dose (0.04 ml), 60 doses, 2.4 ml pre-filled pen
lixisenatide-insulin glargine (Soliqua)	Pre-filled single-patient use pen injector: 100 units/mL insulin glargine and 33 mcg/mL lixisenatide in a 3 mL pen injector
albiglutide(Tanzeum)	Single dose Pen: 30 mg and 50 mg
dulaglutide (Trulicity)	Prefilled single-dose pen 0.75 mg/0.5ml, 1.5 mg /0.5ml; Prefilled single-dose syringe 0.75 mg/0.5ml, 1.5 mg /0.5ml
liraglutide (Victoza)	Multi-Dose Pre-filled Pen: 6 mg/ml, 3 ml pre-filled pen with 2 pens; 6 mg/ml, 3 ml pre-filled pen with 3 pens

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	

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

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.