GLP-1 (glucagon-like peptide-1) Agonists (Adlyxin™, Byetta®, Bydureon™, Bydureon BCise™, Ozempic®, Tanzeum™, Trulicity™, Victoza®) Step Therapy and Quantity Limit Program Summary

This program applies to Commercial, GenPlus and Health Insurance Marketplace formularies.

OBJECTIVE
The intent of the GLP-1 (glucagon-like peptide-1) Agonists [Adlyxin (lixisenatide), Byetta (exenatide), Bydureon (exenatide extended-release), Bydureon BCise (exenatide extended-release), Ozempic (semaglutide), Tanzeum (albiglutide), Trulicity (dulaglutide), and Victoza (liraglutide)] Step Therapy (ST) program is to ensure appropriate selection of patients based on product labeling, and/or clinical guidelines, and/or clinical studies. Appropriate patients for GLP-1 agonist therapy are those who are concurrently receiving or have tried an agent containing metformin or sulfonylurea, insulin, or insulin/GLP-1. The step edit allows continuation of therapy when patient is currently receiving the requested agent. Patients without prerequisite agents in claims history or those who are unable to take a prerequisite agent due to documented intolerance, FDA labeled contraindication, or hypersensitivity will be reviewed when patient-specific documentation has been provided.

TARGET AGENTS
Adlyxin™ (lixisenatide)
Byetta® (exenatide)
Bydureon™ (exenatide extended-release)
Bydureon BCise™ (exenatide extended-release)
Ozempic® (semaglutide)
Tanzeum™ (albiglutide)
Trulicity™ (dulaglutide)
Victoza® (liraglutide)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Target Agents will be approved when BOTH of the following are met:

1. The patient has a diagnosis of type 2 diabetes mellitus
   AND
2. ONE of the following:
   1. The patient's medication history includes one or more of the following antidiabetic agents; an agent containing metformin or sulfonylurea, insulin, or insulin/GLP-1 in the past 90 days
      OR
   2. There is documentation that the patient is currently using the requested agent
      OR
   3. The prescriber states the patient is using the requested agent AND is at risk if therapy is changed
      OR
   4. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to at least one of the following agents: metformin, sulfonylurea, or insulin

Length of approval: 12 months

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NOTE: If Quantity Limit program also applies, please refer to Quantity Limit documents.

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The purpose of Blue Cross and Blue Shield of Alabama's pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.

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FDA APPROVED INDICATIONS AND DOSAGE[1-6,9]

GLP-1 Agonist	Indication	Important limitations for use	Dosage and Administration
Adlyxin (lixisenatide) **Available as:** Starter Pack: For treatment initiation, 1 prefilled green pen of 10 mcg and 1 prefilled burgundy pen of 20 mcg Maintenance Pack: 2 prefilled burgundy pens of 20 mcg	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	• Adlyxin has not been studied in patients with chronic pancreatitis or a history of unexplained pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis • Adlyxin is not a substitute for insulin. Adlyxin is not indicated for use in patients with type 1 diabetes mellitus or for treatment of diabetic ketoacidosis • The concurrent use of Adlyxin with short acting insulin has not been studied and is not recommended • Adlyxin has not been studied in patients with gastroparesis and is not recommended in patients with gastroparesis	• Starting dose of 10 mcg subcutaneously once daily for 14 days. • Increase the dose to the maintenance dose of 20 mcg once daily starting on Day 15.
Byetta (exenatide) Injection **Available as**: 250 mcg/mL in: 5 mcg per dose, 60 doses, 1.2 mL prefilled pen 10 mcg per dose, 60 doses, 2.4 mL prefilled pen	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	• Not a substitute for insulin. Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. • Concurrent use with prandial insulin has not been studied and cannot be recommended. • Byetta has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.	• Inject subcutaneously within 60 minutes prior to morning and evening meals (or before the 2 main meals of the day, approximately 6 hours or more apart). • Initiate at 5 mcg per dose twice daily; increase to 10 mcg twice daily after 1 month based on clinical response.
Bydureon (exenatide extended-release) Injection **Available as**: 2 mg vial in single-dose tray	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	• Not a substitute for insulin. Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. • Concurrent use with insulin has not been studied and cannot be recommended.	• Inject subcutaneously 2 mg once weekly at any time of day, with or without meals. The day of weekly administration can be changed if necessary as long as the last dose was administered 3 or

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GLP-1 Agonist	Indication	Important limitations for use	Dosage and Administration
with syringe of diluent and needle; 4 trays per carton 2 mg single-dose pen supplied in cartons with 4 pens and needle		• Bydureon has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.	more days before. • Injection should be in the abdomen, thigh or upper arm.
Bydureon BCise (exenatide extended release) Injection **Available as:** 2 mg single dose auto-injector supplied in cartons with 4 auto-injectors	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	• Not recommended as first-line therapy for patients inadequately controlled on diet and exercise. • Should not be used to treat type 1 diabetes or diabetic ketoacidosis. • Use with insulin has not been studied and is not recommended. • Bydureon BCise is an extended-release formulation of exenatide. Do not coadminister with other exenatide containing products. • Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.	• Administer 2 mg by subcutaneous injection once every seven days (weekly), at any time of day and with or without meals. • Administer immediately after the dose is prepared.
Ozempic (semaglutide) **Available as:** Single-patient-use-pen, in cartons of one 2 mg pen delivering doses 0.25-0.5 mg per injection; and in cartons of two 2 mg pens delivering 1 mg per injection	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	• Ozempic is not recommended as a first-line therapy for patients who have inadequate glycemic control on diet and exercise because of the uncertain relevance of rodent C-cell tumor findings to humans • Ozempic has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis • Ozempic is not a substitute for insulin. OZEMPIC is not indicated for use in patients with	• Administer once weekly at any time of day, with or without regard to meals. • Initiate at 0.25 mg subcutaneously once weekly. Dose can be increased to 0.5 mg once weekly after 4 weeks, and the increased to 1 mg once weekly after 4 weeks of 0.5 mg once weekly therapy • Inject subcutaneously in the abdomen, thigh, or upper arm.

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GLP-1 Agonist	Indication	Important limitations for use	Dosage and Administration
		type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis, as it would not be effective in these settings	

GLP-1 Agonist	Indication	Important limitations for use	Dosage and Administration
Tanzeum (albiglutide for injection, for subcutaneous (SC) use **Available as:** single-dose pens for injection, in cartons of 4 syringes plus needles, in doses of 30 mg and 50 mg	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	• Tanzeum is not indicated in the treatment of patients with type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis; it is not a substitute for insulin in these patients. • Not recommended as first-line therapy for patients inadequately controlled on diet and exercise. • Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis. • Has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis. Use is not recommended in patients with pre-existing severe gastrointestinal disease. • Has not been studied in combination with prandial insulin.	• Administer once weekly at any time of day, without regard to meals. • Initiate at 30 mg subcutaneously once weekly. Dose can be increased to 50 mg once weekly in patients requiring additional glycemic control. • Inject subcutaneously in the abdomen, thigh, or upper arm.
Trulicity (dulaglutide for SC injection) **Available as:** Single dose pens and prefilled syringes	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	• Not recommended as first-line therapy for patients inadequately • controlled on diet and exercise • Has not been studied in patients with a history of pancreatitis. • Consider another antidiabetic therapy • Not for treatment of type 1 diabetes mellitus or	• Administer once weekly at any time of day • Inject subcutaneously in the abdomen, thigh, or upper arm • Initiate at 0.75 mg subcutaneously once weekly. Dose can be increased to 1.5 mg once weekly for additional glycemic control

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GLP-1 Agonist	Indication	Important limitations for use	Dosage and Administration
		diabetic ketoacidosis. • Not for patients with pre-existing severe gastrointestinal disease. • Has not been studied in combination with basal insulin	
Victoza (liraglutide [rDNA origin] injection), solution for subcutaneous (SC) use **Available as:** Solution for subcutaneous injection, pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL, 3 mL)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	• Victoza is not a substitute for insulin. Victoza should not be used in patients with type 1 diabetes mellitus or for the treatment of or diabetic ketoacidosis, as it would not be effective in these settings. • Concurrent use with prandial insulin has not been studied. • Not recommended as first-line therapy for patients inadequately controlled on diet and exercise. • Has not been studied sufficiently in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.	• Administer once daily at any time of day. • The injection site and timing can be changed without dose adjustment. • Initiate at 0.6 mg per day for one week. This dose is intended to reduce GI symptoms during initial titration, and is not effective for glycemic control. After 1 week, increase the dose to 1.2 mg. If 1.2 mg dose does not result in acceptable glycemic control, dose can be increased to 1.8 mg. • When initiating, consider reducing the dose of concomitantly-administered insulin secretagogues to reduce the risk of hypoglycemia.

CLINICAL RATIONALE

Guidelines[3,4]

Both the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) recommend metformin as the optimal non-insulin first-line drug in type II diabetes mellitus.[6,7] Initial dual non-insulin therapy or insulin therapy may be considered to reduce time to goal treatment targets when A1C is >9%.[6] The AACE recommends metformin plus a second agent when A1C is >7.5%. Guidelines support sulfonylurea (SU), thiazolidinedione (TZD), dipeptidyl peptidase-4 inhibitor (DPP-4), sodium glucose transporter 2 inhibitor (SGLT2), glucagon-like peptide-1 receptor agonist (GLP-1), or insulin (usually basal e.g., NPH, insulin glargine, or insulin detemir) as first line alternatives when metformin cannot be used.[6,7]

Beyond first-line therapy pharmacotherapy choice is based on patient and drug characteristics in order to improve glycemic control and minimize side effects.[6,7] Dual-therapy optimally include combining metformin with either a SU, TZD, DPP-4, SGLT2, GLP-1, or basal insulin.[6] If

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the goal is not met with two-drugs, a third agent may be added albeit combination of complementary mechanisms of action is essential. Notably, insulin is likely to be more effective than most other agents as a third-line therapy, especially symptomatic patients when A1C is very high (e.g., >9.0%).[7]

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7. American Diabetes Association. Standards of medical care in diabetes-2016. Diabetes Care 2016; 39(Supp 1): S1-S112.
8. Garber, A, Abrahamson, M, Barzilay, J et al. Consensus statement by the American association of clinical endocrinologists and American college of endocrinology on the comprehensive type 2 diabetes management algorithm – 2016 executive summary. Endocrin Pract 2015; 22 (No. 1): 84-113.
9. Bydureon BCise prescribing information. AstraZeneca Pharmaceuticals, Inc. October 2017.
10. Ozempic prescribing information. Novo Nordisk. December 2017.

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