Medicaid Drug Use Criteria

Glucagon-Like Peptide 1 Receptor Agonists

- Developed February 2006.
- Revised September 2020; September 2018; September 2016; June 2015; October 2013; December 2011; February 2010; January 2010; August 2006; May 2006.

Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

Prepared by:

- Drug Information Service, UT Health San Antonio
- The College of Pharmacy, the University of Texas at Austin

1 Dosage [*]

1.1 Adults

Incretin hormones such as glucagon-like peptide (GLP-1) are peptides released from gastrointestinal tract cells in response to food ingestion that stimulate glucose-dependent insulin release from the pancreas, decrease glucagon production, and slow gastric emptying. Incretin mimetics, also known as GLP-1

agonists, are FDA-approved as adjunct therapy to diet and exercise to improve glycemic control in adult type 2 diabetics. GLP-1 agonists are not recommended for use as first-line therapy in type 2 diabetes mellitus due to development of malignant thyroid C-cell tumors in rats; these compounds should be used in diabetic patients only when the therapeutic benefits exceed treatment risks. Several GLP-1 agonists have demonstrated cardiovascular benefit in patients with established atherosclerotic cardiovascular disease (ASCVD) including dulaglutide, liraglutide, and the injectable formulation of semaglutide. The oral formulation of semaglutide has not demonstrated the same reduction in cardiovascular outcomes as the injectable formulation. It is recommended to initiate a GLP-1 agonist with demonstrated cardiovascular benefit, in addition to current therapy, in patients with established ASCVD or indicators of high ASCVD risk including age of 55 years or older with coronary, carotid, or lower extremity artery stenosis greater than 50% or left ventricular hypertrophy. Additionally, it is not recommended to initiate a GLP-1 agonist with cardiovascular benefit, in addition to current therapy, in patients with heart failure or chronic kidney disease and an SGLT-2 inhibitor is not tolerated or contraindicated.

GLP-1 agonists should not be administered to patients:

- with type 1 diabetes
- experiencing diabetic ketoacidosis
- receiving prandial insulin therapy
- with a history of pancreatitis
- experiencing hypersensitivity reactions to exenatide or its components
- with severe gastrointestinal disease, including gastroparesis

GLP-1 agonist recommended dosages are summarized in Table 1. Patient profiles containing prescriptions with GLP-1 agonist dosages that exceed these recommendations will be reviewed.

Table 1. Adult Injectable GLP-1 Agonist Maximum Recommended Dosages in type 2 Diabetes Mellitus

Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
dulaglutide (Trulicity®)#	extended-release SC solution; 0.75 mg/0.5 mL, 1.5 mg/0.5mL as single-dose pens or pre-filled syringes	1.5 mg once weekly at any time of day with or without meals

Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
exenatide (Byetta®)	regular-release SC solution; 5 mcg/0.02 mL pen, 10 mcg/0.04 mL pen*	5 mcg SC twice daily initially within 60 minutes *prior to* the morning and evening meals, or prior to the two main meals of the day spaced six hours or more apart; dose may be increased to 10 mcg twice daily *prior to* the morning and evening meals (or the two main meals of the day, spaced six hours or more apart) after one month of therapy based on clinical response
exenatide (Bydureon®)	extended-release SC suspension; 2 mg/0.65 mL mixed in syringe; 2 mg/0.65 mL pen+	2 mg once every 7 days (weekly) at any time of day, with or without meals
liraglutide (Victoza®)#	SC solution; multi-dose pen (18 mg/3 mL) that delivers 0.6 mg, 1.2 mg, or 1.8 mg	1.8 mg/day at any time of day with or without meals
lixisenatide (Adlyxin®)	SC solution; 150 mcg/3 mL (starter pen) delivers 14 doses of 10 mcg; 300 mcg/3 mL (maintenance pre-filled pen) delivers 14 doses of 20 mcg	20 mcg/day at any time of day with or without meals
semaglutide (Ozempic®)#	SC solution; multi-dose pen available as either 0.25 mg# for therapy titration (2 mg/1.5 mL) or 0.5 mg per dose (2 mg/1.5 mL) - package of 1 pen to deliver 6 weeks of therapy (4 weeks titration and 2 weeks of 0.5 mg dose); or 1 mg per dose (2 mg/1.5 mL) – package size of 2 pens to deliver 4 weeks of therapy	0.25 mg# SC once weekly x 4 weeks, then titrate upward to 0.5 mg SC once weekly; if glycemic control not achieved, may titrate to a maximum of 1 mg SC once weekly

- SC = subcutaneous
- #Indicates that therapy is approved for reduction of cardiovascular mortality and cardiovascular events in patients with type 2 diabetes mellitus and cardiovascular disease
- *each exenatide regular-release pen provides 60 doses of medication
- +each exenatide extended-release pen is single-use pen; supplied in carton of 4 pens
- #0.25 mg semaglutide dose is for therapy titration only – does not provide glycemic control

Table 2. Adult Oral GLP-1 Agonist Maximum Recommended Dosages in type 2 Diabetes Mellitus

Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
Semaglutide (Rybelsus®)	3 mg, 7 mg, 14 mg oral tablets	14 mg/day

1.2 Pediatrics

GLP-1 agonists are not recommended for use in children as safety and efficacy in pediatric patients have not been established.

2 Duration of Therapy

GLP-1 agonists are indicated for the management of type 2 diabetes mellitus and may be continued indefinitely, as control of blood glucose is a chronic, lifelong process.

3 Duplicative Therapy [*]

Adjunctive administration of multiple GLP-1 agonists is not recommended due to increased risk for adverse events with no additional therapeutic benefit. Exenatide regular-release should be discontinued prior to initiating exenatide extended-release therapy. Patient profiles containing prescriptions for multiple GLP-1 agonists will be reviewed.

4 Drug-Drug Interactions [*]

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically relevant for GLP-1 agonists are summarized in Table 2. Only those drug-drug interactions identified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed.

Table 3. GLP-1 Receptor Agonist Drug-Drug Interactions

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level*
antidiabetic agents	fluoroquinolones	adjunctive administration may result in blood glucose disturbances and increased risk for hyper- or hypoglycemia due to an unknown mechanism	closely monitor blood glucose levels and adjust antidiabetic doses as needed; doses may also require adjustments with fluoroquinolone discontinuation	major (DrugReax) 3-moderate (CP)
antidiabetic agents	somatostatin analogues (SAs) (e.g., octreotide, pasireotide)	concurrent use may impair glucose regulation as SAs inhibit insulin and glucagon secretion; substantially increased blood glucose levels may result	monitor closely for changes in blood glucose control before and throughout SA therapy; adjust antidiabetic doses as needed	major (DrugReax) 2-major (CP)
exenatide	warfarin	concurrent administration may result in increased international normalized ratio (INR), sometimes with associated bleeding; mechanism unknown	closely monitor for changes in INR and bleeding with exenatide/warfarin drug combination	moderate (DrugReax) 3-moderate (CP)
GLP-1 agonists	gastric stimulants (e.g., metoclopramide, tegaserod)	concurrent administration may attenuate pharmacologic effects due to competing effects from both agents	monitor blood glucose levels and adjust antidiabetic doses as needed	3-moderate (CP)
GLP-1 agonists	insulin secretagogues (e.g., sulfonylureas, insulin)	adjunctive administration may lead to increased hypoglycemia due to additive glucose-lowering effects	avoid use, if possible; if combined use needed, adjust insulin doses and closely monitor blood glucose levels	major, moderate (DrugReax) 2-major, 3-moderate (C)P)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level*
GLP-1 agonists	oral contraceptives (OCs)	concurrent administration may reduce OC serum levels and reduce efficacy as GLP-1 agonists delay gastric emptying; also, estrogens and progestins impair glucose tolerance	use cautiously together; administer OCs at least 1 hour before GLP-1 agonists and monitor for glycemic control	lixisenatide – major (DrugReax) 3-moderate (CP)
GLP-1 agonists	oral medications with hypoglycemic effects (e.g., oral antidiabetic agents, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, fibric acid derivatives, salicylates, sulfonamide antibiotics)	concomitant administration may result in enhanced hypoglycemic pharmacologic and adverse effects	monitor blood glucose levels closely and adjust dosages as necessary if drug combination required to minimize excessive hypoglycemia and associated adverse events	3-moderate (CP)
GLP-1 agonists	oral medications that slow gastrointestinal motility (e.g., opiate agonists, tricyclic antidepressants, antimuscarinics, diphenoxylate)	adjunctive administration may potentiate GLP-1 agonist pharmacologic effects, including additional blood glucose reductions and hypoglycemia risk	use cautiously together	undetermined

- * CP = Clinical Pharmacology

5 References

1. American Diabetes Association. 10. Cardiovascular disease and risk management: standards of medical care in diabetes -2020. Diabetes Care. 2020;43(Suppl. 1):S111–S134.

2. Sheahan KH, Wahlberg EA, Gilbert MP. An overview of GLP-1 agonists and recent cardiovascular outcomes trials. Postgrad Med J. 2020; 96: 156-161.
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. Accessed August 13, 2020.
4. IMB Micromedex® DRUGDEX® (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Accessed August 13, 2020.
5. Facts & Comparisons eAnswers [database online]. Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2020. Accessed August 14, 2020.
6. Exenatide regular-release (Byetta®) package insert. AstraZeneca Pharmaceuticals, February 2020.
7. Exenatide extended-release (Bydureon®) package insert. AstraZeneca Pharmaceuticals, February 2020.
8. Dulaglutide subcutaneous injection (Trulicity®) package insert. Eli Lilly and Company, February 2020.
9. Liraglutide subcutaneous injection (Victoza®) package insert. Novo Nordisk, September 2019.
10. Lixisenatide subcutaneous injection (Adlyxin™) package insert. Sanofi-Aventis, January 2019.
11. Semaglutide subcutaneous injection (Ozempic®) package insert. Novo Nordisk, January 2020.
12. Semaglutide oral tablets (Rybelsus®) package insert. Novo Nordisk, January 2020.
13. Smits MM, van Raalte DH, Tonneijck L, et al. GLP-1 based therapies: clinical implications for gastroenterologists. Gut. 2016;65:702-11.
14. DeFronzo RA, Ratner RE, Han J, et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care. 2005;28:1092-1100.
15. Buse JB, Henry RR, Han J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care. 2004;27:2628-35.
16. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care. 2005;28:1083-91.
17. Moretto TJ, Milton DR, Ridge TD, et al. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naive patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther. 2008;30(8):1448-60.

18. Zarowitz BJ, Conner C. The intersection of safety and adherence: new incretin-based therapies in patients with type 2 diabetes mellitus. Pharmacotherapy. 2009;29(12 Pt 2):55S-67S.
19. Davies MJ, Donnelly R, Barnett AH, et al. Exenatide compared with long-acting insulin to achieve glycaemic control with minimal weight gain in patients with type 2 diabetes: results of the Helping Evaluate Exenatide in patients with diabetes compared with Long-Acting insulin (HEELA) study. Diabetes Obes Metab. 2009;11(12):1153-62.
20. Bunck MC, Diamant M, Corner A, et al. One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. Diabetes Care. 2009;32(5):762-8.
21. Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. Ann Intern Med. 2011;154(2):103-12.
22. Hurren KM, Pinell NR. Drug-drug interactions with glucagon-like peptide-I receptor agonists. Ann Pharmacother. 2012;48:710-7.
23. Drab SR. Incretin-based therapies for type 2 diabetes mellitus: current status and future prospects. Pharmacotherapy. 2010;30(6):609-24.
24. Murphy CE. Review of the safety and efficacy of exenatide once weekly for the treatment of type 2 diabetes mellitus. Ann Pharmacother. 2012;46:812-21.
25. Aguilar AB. Evaluating treatment algorithms for the management of patients with type 2 diabetes mellitus: a perspective on the definition of treatment success. Clin Ther. 2011;33(4):408-24.
26. Davidson JA, Nikkel C, Grimm M. Exenatide once weekly: opportunities in the primary care setting. Postgrad Med. 2013;125(3):68-78.
27. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes -2020. Diabetes Care. 2020;43(Suppl. 1):S98–S110.