Texas Vendor Drug Program

Drug Use Criteria: Glucagon-Like Peptide 1 Receptor Agonists

Publication History

1. Developed February 2006.
2. Revised **October 2022;** September 2020; September 2018; September 2016; June 2015; October 2013; December 2011; February 2010; January 2010; August 2006; May 2006.

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

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1 Dosage

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.[1,2] Incretin mimetics, also known as GLP-1 agonists, are FDA-approved as adjunct therapy to diet and exercise to improve glycemic control **in patients with type 2 diabetes**.[1-12] **GLP-1 agonists are appropriate first-line therapies in patients with type 2 diabetes who have or are at high risk of developing atherosclerotic cardiovascular disease and/ or chronic kidney disease.**[13] 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.[1-3,6,9] The oral formulation of semaglutide has not demonstrated the same reduction in cardiovascular outcomes as the injectable formulation.[14] 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.[15] **Two GLP-1 agonists, Saxenda® (liraglutide) and Wegovy® (semaglutide), are approved for chronic weight management in patients with a BMI of 30 kg/m^2 or greater, or in patients with a BMI of 27 kg/m^2 or greater with the presence of at least one weight-related comorbidity, such as hypertension, type 2 diabetes, or dyslipidemia**.[1,2,7,10]

All GLP-1 agonists have been found to cause c-cell tumors in rodent models, but the human relevance has not been determined. All agents except for Byetta® (exenatide) and Adylxin® (lixisenatide) have a black box warning for risk of thyroid C-cell tumors, and they are contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC). These agents are also contraindicated in patients with Multiple Endocrine Neoplasia syndrome 2 (MEN 2). Additionally, all GLP-1 agonists have a warning for acute pancreatitis, and patients should not resume therapy with a GLP-1 agonist if acute pancreatitis has occurred.

GLP-1 agonists should generally be avoided in patients who are pregnant unless the potential benefit outweighs the potential risk to the fetus. Pregnancy is a contraindication to therapy for the following agents; Saxenda® (liraglutide), Wegovy® (semaglutide), Rybelsus® (semaglutide), and Ozempic® (semaglutide).[1,2,7,9-11]

Additional warnings for this drug class include hypoglycemia when used in combination with an insulin secretagogue or insulin, acute kidney injury or renal impairment, and hypersensitivity reactions. GLP-1 agonists have not been studied in patients with gastroparesis, and all drugs within this class, except for liraglutide and semaglutide, recommend against use in patients with preexisting gastroparesis.[1-12]

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[1-11]

Drug Name	Dosage Form/ Strength	Treatment Indications	Maximum Recommended Dosage
dulaglutide (Trulicity®)	extended-release SC solution; 0.75 mg/0.5 mL, 1.5 mg/0.5mL, **3 mg/0.5 mL, and 4.5 mg/0.5 mL** as single-dose pens	type 2 diabetes mellitus; reduction of CV mortality	**0.75 mg SC once weekly, then titrate to 1.5 mg once weekly; if glycemic control not achieved, may titrate up every 4 weeks to a maximum of 4.5 mg once weekly**

Drug Name	Dosage Form/ Strength	Treatment Indications	Maximum Recommended Dosage
exenatide (Byetta®)	regular-release SC solution; 5 mcg/0.02 mL pen, 10 mcg/0.04 mL pen*	type 2 diabetes mellitus	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 ® BCise**	extended-release SC injectable suspension; **2 mg/0.85 mL single dose autoinjector**+	type 2 diabetes mellitus	**2 mg SC once weekly** at any time of day, with or without meals
liraglutide (Victoza®)	SC solution; multi-dose pen (18 mg/3 mL) that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg	type 2 diabetes mellitus; reduction of CV mortality	**0.6 mg@ SC daily for at least one week; titrate to 1.2 mg daily, up to maximum of 1.8 mg daily**
liraglutide (Saxenda ®)	**SC solution; multi-dose pen (18 mg/3 mL) that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3 mg**	**chronic weight management**	**0.6 mg SC daily for at least one week, followed by an increase in increments of 0.6 mg every week up to maximum of 3 mg SC mg daily**
lixisenatide (Adlyxin®)	**SC solution; multi-dose pen available as either 10 mcg per dose (150 mcg/3 mL) or 20 mcg per dose (300 mcg/3 mL)**	type 2 diabetes mellitus	**10 mcg SC once daily for 14 days; on day 15 increase dose to 20 mcg daily**

Drug Name	Dosage Form/ Strength	Treatment Indications	Maximum Recommended Dosage
semaglutide (Ozempic®)	**SC solution; multi-dose pen available as either 0.25 mg or 0.5 mg per dose (2 mg/1.5 mL), 1 mg per dose (4 mg/3 mL), or 2 mg per dose (8 mg/3 mL)**	type 2 diabetes mellitus; reduction of CV mortality	0.25 mg[@] SC once weekly x 4 weeks, then titrate upward to 0.5 mg once weekly**; if glycemic control not achieved after 4 weeks, may titrate to 1 mg once weekly; if glycemic control not achieved after 4 weeks, may titrate to a maximum of 2 mg once weekly**
semaglutide (Wegovy®)	**SC solution; single-dose pen that delivers doses of 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, or 2.4 mg**	**chronic weight management**	**0.25 mg SC weekly for at least 4 weeks, followed by a dose escalation every 4 weeks up to maximum of 2.4 mg daily**
tirzepatide (Mounjaro®)	**SC solution; single dose pens available as 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL**	**type 2 diabetes mellitus**	**2.5 mg[@] SC once weekly x 4 weeks, then titrate upward to 5 mg SC once weekly; if glycemic control not achieved, may titrate up by 2.5 mg increments every 4 weeks to a maximum of 15 mg SC once weekly**

SC = subcutaneous
**each exenatide regular-release pen provides 60 doses of medication*
*[+]each exenatide extended-release **autoinjector** is single-dose; supplied in carton of 4 pens*
[@]indicates 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[1,2,11]

Drug Name	Dosage Form/ Strength	Treatment Indications	Maximum Recommended Dosage
semaglutide (Rybelsus®)	3 mg, 7 mg, 14 mg oral tablets	**type 2 diabetes mellitus**	**3 mg daily for 30 days, if glycemic control not achieved, may titrate up to 7 mg daily, may titrate after 30 days to a maximum of 14 mg daily**

Pediatrics

The use of GLP-1 agonists Victoza® (liraglutide) and Bydureon® (exenatide) have been proven to be safe and effective as an adjunct to diet and exercise to improve glycemic control in pediatric patients that are 10 years of age and older with established Type 2 diabetes.[1,2,5,6] Saxenda® (liraglutide) is approved as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in patients 12 years of age and older weighing over 60 kg and an initial BMI of 30 kg/m^2 or greater.[1,2,7]

Table 3. Pediatric Injectable GLP-1 Agonist Maximum Recommended Dosages[1,2,5-7]

Drug Name	Dosage Form/ Strength	Treatment Indications	Maximum Recommended Dosage
exenatide (Bydureon® BCise)	**extended-release SC injectable suspension; 2 mg/0.85 mL single dose autoinjector+**	**type 2 diabetes mellitus**	***10 years to 17 years:* 2 mg SC once 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**	**type 2 diabetes mellitus**	***10 years to 17 years:* 0.6 mg SC daily for at least one week; if glycemic control is not achieved, may titrate up to 1.2 mg SC daily, after one week may increase to maximum of 1.8 mg daily**

Drug Name	Dosage Form/ Strength	Treatment Indications	Maximum Recommended Dosage
liraglutide (Saxenda®)	**SC solution; multi-dose pen (18 mg/3 mL) that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3 mg**	**chronic weight management**	***12 years to 17 years:*** **0.6 mg SC daily for at least one week, followed by an increase in increments of 0.6 mg every week up to maximum of 3 mg daily**

[+]***each exenatide extended-release autoinjector is single-dose; supplied in carton of 4 pens***

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. **There is no basis for limiting the duration of treatment for GLP-1 agonists in patients using this medication for chronic weight management if it remains beneficial for weight loss and is not causing intolerable side effects.**[16]

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, **semaglutide, lixisenatide, tirzepatide**	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 secretagogue** or 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)
tirzepatide	**oral contraceptives (OCs)**	**concurrent administration may reduce OC serum levels and reduce efficacy as GIP/GLP-1 agonists delay gastric emptying; the impact the greatest after the first dose, and this effect diminishes with subsequent doses**	**use non-oral contraceptive or add barrier method for the 4 weeks after initiation and 4 weeks after each dose escalation**	**2-major (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)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level*
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

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