Wyoming Drug Utilization Review

Type 2 Diabetes Mellitus: Glucagonlike peptide-1 receptor agonists

Written by Huong Pham, PharmD candidate, 2021

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disease characterized by the loss of pancreatic b-cells function and decrease in insulin level (1). Due to the chronic nature of the disease, most patients will require multiple anti-diabetic agents for the optimal management of T2DM. While metformin remains as the first-line therapy, a glucagonlike peptide-1 receptor agonist (GLP-1 RAs) is an appropriate choice as add-on therapy for the management of T2DM (1).

GLP-1 RAs are a class of medications used in the management of T2DM, in addition to diet and exercise (2). GLP-1 RAs reduce post-prandial glucose (PPG) and fasting plasma glucose (FPG)(2) by stimulating glucose-dependent insulin release from pancreatic b-cells, inhibiting inappropriate glucagon release after meals, slowing gastric emptying, and decreasing food intake (1). GLP-1 RAs are recommended as add on therapy for patients who have not achieved a HbA1c goal of less than 6.5% after 3 months of monotherapy or dual therapy with other agents (3). GLP-1 RAs should be considered before the addition of prandial insulin in patients inadequately controlled with basal insulin (3). Wyoming Medicaid requires a 90-day trial of metformin before approval of a GLP-1 RA (4). GLP-1 RAs can be used in combination with metformin, thiazolidinediones, sulfonylureas, SGLT-2 inhibitors and insulin (1). GLP-1 RAs should not be used in combination with dipeptidyl peptidase IV (DPP-4) inhibitors due to the lack of additive efficacy (2).

GLP-1 RAs are effective in lowering HbA1c levels by 0.5% to 1.5% (1). Additional benefits of GLP-1 RAs include: lower risk of hypoglycemia, weight loss, and decrease in major cardiovascular events (3). Cardiovascular event decreases include: non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality (5). Dulaglutide, liraglutide, and semaglutide are indicated for patients with T2DM and established cardiovascular disease (2). Exenatide twice daily appears to be less effective at lowering HbA1c, has poorer glycemic control, and increased nausea compared to long-acting GLP-1 RAs (1). Short-acting GLP-1 RAs are appropriate for patients presenting with predominantly postprandial hyperglycemia (5). Long-acting GLP-1 RAs are appropriate for patients presenting with predominantly fasting hyperglycemia (5).

Common adverse events of GLP-1 RAs include: loss of appetite, diarrhea, nausea, vomiting,

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abdominal pain, fatigue, and injection site irritation (2). Gastrointestinal effects are dose-related, therefore titration is recommended (3). Cases of acute pancreatitis associated with the use of GLP-1 RAs have been reported (2). Signs of acute pancreatitis include: severe abdominal pain, back pain, nausea or vomiting. For most GLP-1 RAs, with the exception of lixisenatide, thyroid C-cell tumors have developed in rodents. It is currently unknown whether these animal studies translate to humans. These GLP-1 RAs therefore contain a boxed warning stating the risk of thyroid C-cell tumor, and all are contradicted in patients with a family history of medullary thyroid carcinoma (MTC) and multiple endocrine neoplasia syndrome type 2 (MEN 2) (2).

Prior to the availability of semaglutide oral tablets, GLP-1 RA formulations required subcutaneous injection (2). Injectable formulations require patients to inject into the upper arm, thigh, or abdomen. Patients should be advised to rotate injection sites (2). All injectable formulations are required to be stored in a refrigerator prior to initial use (5). Additional comparative information between GLP-1 RAs is provided in Table 1. Patient education of the prescribed GLP-1 RA is important to ensure appropriate delivery of the medication and maximize therapeutic effects. Subcutaneous administration may be a limiting factor for GLP-1 RAs (6). Although semaglutide oral tablets are now available, there is a lack of comparative efficacy data to other GLP-1 RAs (1). Semaglutide tablet cardiovascular benefits are not yet established (5).

GLP-1 RAs are effective at lowering HbA1c level in addition to diet and exercise. GLP-1 RAs are recommended as an add-on agent for patients with T2DM, currently on monotherapy or dual therapy that have not reached HbA1c goal. GLP-1 RAs are especially beneficial for patients with T2DM that desire weight loss or have established cardiovascular disease. Gastrointestinal adverse effects are the most common and appear to be dose related. Dose titration may decrease those adverse effects. Formulations of GLP-1 RAs vary in frequency, administration, and storage, therefore patients should be counseled to ensure optimal outcomes.

Table 1: Comparisons between GLP-2 receptor agonists[1,4,5]

Generic (Brand)	Formulation and Strengths	Storage	Frequency & Administrations	Adjustment	Short-Term Weight Loss
Dulaglutide (Trulicity)	Single-dose pen-injector (needles included) 0.75 mg/0.02 mL 1.5 mg/0.5 mL	May be stored at room temperature for 14 days	Once weekly No mixing required	Renal: No Hepatic: No	~2.5 kg
Exenatide (Byetta)	Multi-dose pen-injector (needles not included) 5 mcg/0.02 mL 10 mcg/0.04 mL	After first use, store at room temperature Discard 30 days after first use	Twice daily Prime pen before first use Administer 60 minutes before meals No mixing required	Renal: Caution Hepatic: No	~2 kg
Exenatide ER (Bydureon BCise, Bydureon Pen, Bydureon)	Single-dose auto-injector Single-dose dual chamber pen Single-dose vial (needles included) 2 mg	Dual chamber pen and auto-injector can be kept at room temperature for up to 4 weeks Allow auto-injector and pen to come to room temperature before administration (15 minutes)	Once weekly Administer immediately after reconstitution or mixing	Renal: Caution Hepatic: No	~1.4-2.5 kg
Liraglutide (Victoza)	Multi-dose pen-injector (needles not included) 6 mg/3 mL	After first use, store at room temperature Discard 30 days after first use	Once daily. Administer without regards to meals No mixing required	Renal: Caution Hepatic: Caution	~2.5 kg
Lixisenatide (Adlyxin)	Pen-injector (needles not included) 10 mcg/0.2 mL 20 mcg/0.2 mL	After first use, store at room temperature Discard 14 days after first use	Once daily Administer within one hour before the first meal of the day No mixing required	Renal: Caution Hepatic: No	~2 kg
Semaglutide (Ozempic)	Multi-dose pen-injector (needles included) 2 mg/1.5 mL	After first use, stored at room temperature. Discard 56 days after first use.	Once weekly Administer without regards to meals No mixing required	Renal: No Hepatic: No	~4 kg
Semaglutide (Rybelsus)	Oral tablet 3 mg, 7 mg, 14 mg	Store at room temperature in original blister card Protect tablets from moisture	Once daily. Take tablet on empty stomach at least 30 minutes before first food, beverage, or other oral medications Take with no more than 4 ounces of water	Renal: No Hepatic: No	~2.5 kg

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6. Comparison of GLP-1 agonists. Clinical resource. Pharmacist's Letter/Prescriber's Letter. 2019;35(8):350807. Stockton (CA): Therapeutic Research Center; 2020. Available from: https://pharmacist-therapeuticresearch-com. Accessed: June 22, 2020.

The P&T Committee met for its quarterly business meeting on November 4, 2021

Highlights of this meeting include:

- Change Healthcare began processing prior authorization requests for physician-administered drugs on October 25, 2021. Additional information can be found at www.wymedicaid.org.
- Antipsychotics approved for adjunctive treatment for major depressive disorder will be approved after a trial of one preferred medication (currently aripiprazole). Patients will be required to be on concurrent antidepressant therapy.
- Kerendia will require a trial and failure of eplerenone OR spironolactone AND an SGLT2 inhibitor for at least 4 weeks each in the last 12 months. Current use of one of these medications will be required.
- Bylvay will be limited to indication.
- Brexafemme will be approved for patients who have an allergy or contraindication to fluconazole or have failed fluconazole. Documentation of a pregnancy test or other verification that the patient is not pregnant will be required.
- Lybalvi use will require prior authorization with documentation of drug test showing patient is not on prescription or illicit opioids.
- The draft Preferred Drug List for 2022 is available for review and public comment at www.uwyo.edu/DUR. Any comments should be received prior to December 15, 2021.

The proposed prior authorization criteria are open for public comment. Comments may be sent by email to alewis13@uwyo.edu or by mail to: Wyoming Drug Utilization Review Board
Dept. 3375, 1000 E. University Avenue
Laramie, WY 82071.

Comments should be received prior to December 15, 2021.

The next P&T Committee meeting will be held February 10, 2022 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

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