

Glucagon-Like Peptide-1 Receptor Agonists (GLP1RAs) Non-Insulin Diabetes Drugs

Executive Summary

- All GLP1RAs are currently uniform formulary and step therapy applies to the subclass. Patients must first try metformin or a sulfonyleurea (SU) prior to using a GLP1RA. Use of GLP1RAs in patients without a history of diabetes for the indication of obesity is not a covered benefit.
- There are currently five GLP1RAs available in the United States, including Byetta (exenatide twice daily), Bydureon (exenatide once weekly), Victoza (liraglutide), Tanzeum (albiglutide), and Trulicity (dulaglutide).
- Bydureon, Tanzeum, and Trulicity are dosed once weekly. Byetta is given twice daily and Victoza is given once daily.
- When compared head-to-head, there is no clinically significant difference between the GLP1RAs and their effect on glycemic control.
- Weight loss was observed in all seven head-to-head studies. When used as monotherapy or as an add-on agent, a 2-3 kg weight loss can be expected.
- GLP1RAs showed no change or provided small improvements in blood pressure.
- GLP1RAs have little effect on or may improve lipid parameters.
- All GLP1RAs are contraindicated in patients with history of pancreatitis.
- There is a black box warning for medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 in all agents except Byetta.
- Nausea is the most common adverse event among all the GLP1RAs.
- Tanzeum has the lowest incidence of nausea (11.1%) compared to Bydureon (14.4%), Victoza (22.7%), Trulicity (12.1% to 21.1%), or Byetta (29.9%).
- There are no completed trials with any FDA-approved GLP1RA that assesses long-term cardiovascular (CV) outcomes. However, CV safety studies are underway.
- Bydureon, Tanzeum, and Trulicity have the advantage of once weekly dosing.
- Tanzeum and Trulicity have an advantage in offering a smaller needle size for patient convenience.
- Trulicity, Byetta, and Victoza have an advantage in that they do not require mixing prior to administration.

Table 1: Current Formulary Status

GLP1RAs		
BCF	None	
UF	Exenatide BID (Byetta) Exenatide QW (Bydureon) Liraglutide (Victoza) Albiglutide (Tanzeum)	Must try metformin or a SU first; Byetta, Bydureon, Victoza or Tanzeum are second-line agents; 180-day look back
NF	None	

Note: Dulaglutide (Trulicity) has not been previously reviewed.

Table 2: GLP1RAs Available in the United States¹⁻⁵

Active Ingredient	Brand (Manufacturer)	Strengths	FDA Approval Date	Patent Exp Date
Dulaglutide	Trulicity (Eli Lilly)	0.75, 1.5 mg/0.5 mL	09/18/2014	-
Albiglutide	Tanzeum (GlaxoSmithKline)	30 mg, 50 mg	04/15/2014	-
Exenatide	Byetta (AstraZeneca)	5 mcg – 300 mcg/1.2 mL 10 mcg – 600 mcg/2.4 mL	04/28/2005	12/01/2016
Exenatide Once Weekly	Bydureon (AstraZeneca)	2 mg/0.65 mL (3.08 mg/mL)	01/27/2012	12/2016 - 2025
Liraglutide	Victoza (Novo Nordisk)	0.6 mg, 1.2 mg, 1.8 mg 18 mg/3 mL	01/25/2010	08/22/2017

Indications

The GLP1RAs are all indicated for monotherapy as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus. They are not recommended for use as first-line therapy in patients inadequately controlled with diet and exercise. Byetta is the only GLP1RA that has an indication for use in combination with insulin.¹⁻⁵

Efficacy

Due to the overwhelmingly number of studies for the safety and efficacy of the GLP1RA class, this review will focus on head-to-head GLP1RA studies and one systematic review.⁶⁻¹³ Table 3 summarizes the seven head-to-head GLP1RA studies of the currently available agents in the United States:

- LEAD 6 (liraglutide versus exenatide BID)
- DURATION 1 (exenatide QW versus exenatide BID)
- DURATION 5 (exenatide QW versus exenatide BID)
- DURATION 6 (exenatide QW versus liraglutide)
- HARMONY 7 (albiglutide versus liraglutide)
- AWARD 6 (dulaglutide versus liraglutide)
- AWARD 1 (dulaglutide versus exenatide)

The studies ranged from 24 to 52 weeks and the primary efficacy measure most commonly reported in GLP1RA studies was change in glycosylated hemoglobin where a 0.5% reduction is considered the minimal clinically important difference. Secondary outcomes such as blood pressure, lipids, and weight were also evaluated.

Table 3: Results of GLP1RA Head-to-Head Trials^{6-11,13}

Study	Duration (weeks)	Treatment Arms	Δ HbA1c (%)	HbA1c < 7% (%)	Δ FPG (mg/dL)	Δ in Body Wt (kg)
LEAD-6 ⁹	26	LIR 1.8 + OHA	-1.12 \pm 0.08	54	-29	-3.24
		Exen 10 mcg BID + OHA	-0.79 \pm 0.08	43	-10.8	-2.87
DURATION-1 ⁷	30	EQW 2 mg	-1.9	71	-41.0	-3.7
		ExBID 10 μ g	-1.5	61	-25.0	-3.6
DURATION-1 ⁷	52	EQW 2 mg	-2.0	71	-47.0	-4.1
		ExBID 10 μ g \rightarrow QW2 mg	-2.0	71	-43.0	-4.5
DURATION-5 ⁶	24	EQW 2 mg	-1.6	58.1	-35.0	-2.3
		ExBID 5 μ g \rightarrow 10 μ g	-0.9	30.1	-12.0	-1.4
DURATION-6 ⁸	26	EQW 2 mg	-1.28	52.3	-32.0	-2.7
		LIR 1.8 mg	-1.48	60.2	-38.0	-3.6
HARMON-7 ¹¹	32	TAN 30 mg \rightarrow 50 mg at wk 6	-0.78	42.2	-21.98	-0.64
		Liraglutide 0.6 mg \rightarrow 1.8 mg at wk 2	-0.99	51.7	-30.27	-2.19
AWARD-6 ¹⁰	26	DUL 1.5 mg	-1.42 p<0.0001(NI)	68	-34.74	-2.9
		LIRA 1.8 mg	-1.36	68	p<0.0001 (NI) -34.20	-3.6
AWARD-1 ¹³	52	<u>Week 26</u>				
		DUL 1.5 mg	-1.51 p<0.001	78 p<0.001	-43	-1.3
		DUL 0.75 mg	-1.30 p<0.001	68 p<0.001	-34	-0.2
		EXEN 100 mg	-0.99 p<0.001	52 p<0.001	-24	-1.1
		PBO	-0.46	43	-5	1.2

Table 4: Other Factors¹⁻⁵

Parameter	Trulicity	Byetta	Bydureon	Victoza	Tanzeum
Frequency of administration	Once weekly	Twice daily	Once weekly	Once daily	Once weekly
Strengths	0.75 mg, 1.5 mg	5mcg,10mcg	2mg	0.6 mg, 1.2 mg, 1.8 mg	30 mg, 50 mg
Package Sizes	4-pack of pre-filled single-dose pens	1.2 mL and 2.4 mL pre-filled pens	Carton of 4 .65 mL pre-filled single-dose trays or 4 single-dose pens	2-pack and 3-pack 3 mL pre-filled, multi-dose pens	1- or 4-pack carton of single-dose pens
Needle Included	Yes, one 29G	No	Yes*, two 23G 5/16" (for vial) or one custom 23G 9/32" (for pen, NO spare)	No	Yes, one or four 29G 5mm, thin wall
Mixing Required	No	No	Yes	No	Yes
Pre-Injection Waiting Time	No	No	Kit – At least 15 mins Pen – No	No	Yes (15-30 min)

References

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Abbreviations

The following abbreviations are used in this review:

HbA1c	– glycosylated hemoglobin
CV	– cardiovascular
FPG	– fasting plasma glucose
GLP1RAs	– glucagon-like peptide-1 receptor agonists
SU	– sulfonylurea