

MTF Formulary Management for the Glucagon-Like Peptide-1 Receptor Agonists (GLP1RAs)

Defense Health Agency Pharmacy Operations Division

Bottom Line

- Exenatide (Bydureon) remains on the BCF and the new Bydureon BCise formulation was added to the BCF, based on cost effectiveness.
- Albiglutide (Tanzeum) will be discontinued from the market by August 2018; it is now non formulary. Dulaglutide (Trulicity) has replaced the formulary position previously occupied by Tanzeum.
- Byetta, Victoza, Adlyxin, Tanzeum, and Ozempic are nonformulary and non-step preferred.
- Bydureon/BCise and Trulicity are the step-preferred GLP1RAs. All new and current users must first try Bydureon/BCise and Trulicity (once weekly dosing) before using Byetta (BID dosing), Victoza, Adlyxin (QD dosing), or Ozempic (weekly dosing).
- There are no dosage conversion charts available for the GLP1RAs. When transitioning patients to Bydureon/Bydureon BCise, only one dose (2mg) exists and no titration is required. Consider reserving Trulicity for patients who experience nodules with Bydureon/Bydureon BCise, or those with renal dysfunction.
- Additionally, patients must first try metformin before using a GLP1RA.
- Bydureon/Bydureon BCise are the most cost effective GLP1RAs, followed by Trulicity.
- There are still a significant number of MTF patients on Victoza; if these patients remain on Victoza, the excess costs to DoD will be approximately \$9 million annually at the MTFs alone.

Uniform Formulary Decision: The Director, DHA, approved the recommendations from the February 2018 DoD P&T Committee meeting on April 24, 2018. Implementation will occur by July 25, 2018.

Uniform Formulary (UF) Agents		Nonformulary Agents
BCF drugs – MTFs <u>must</u> have on formulary	MTFs <u>may</u> have on formulary	MTFs <u>must not</u> have on formulary
<u>Step-Preferred</u> Exenatide Q Week (Bydureon and Bydureon BCise)	<u>Step-Preferred</u> Dulaglutide (Trulicity)	<u>Non Step-Preferred</u> Exenatide BID (Byetta) Liraglutide (Victoza) Albiglutide (Tanzeum) Lixisenatide (Adlyxin) Semaglutide (Ozempic)
Step Therapy applies to ALL (new and current) users of the GLP1RAs; no grandfathering applies for any user. See below for detailed criteria.		

Clinical Summary

- Metformin remains the first-line treatment in all type 2 diabetes mellitus (T2DM) patients unless contraindications exist, based on positive outcomes data from the UKPDS trial, cost-effectiveness, and current DM guidelines (American Diabetes Association, American Association of Clinical Endocrinologists, and the VA/DoD).
- When used as monotherapy or in combination with other oral agents, the GLP1RAs decrease hemoglobin A1c (A1c) on average approximately 1% to 2% from baseline. They are not first-line therapies.
- Patients are likely to experience weight loss with use of any GLP1RA. When used as monotherapy or as an add-on agent, patients can expect a 2-3 kg weight loss.
- GLP1RAs show no change or provide small improvements in blood pressure and lipid profiles.

Product Information

- **Bydureon BCise** is a new easy-to-use autoinjector formulation that is as effective as Bydureon in lowering A1c. It does not require mixing. **Patients currently on Bydureon can remain on therapy, or transition to the new**

BCise autoinjector. Use this video to help counsel patients how to use Bydureon BCise autoinjector.
<https://www.bydureon.com/using-bcise/how-to-use-bydureon-bcise.html>.

- Advantages of Bydureon/Bydureon BCise include the once weekly dosing, lack of a requirement for dosage titration, and the low incidence of nausea.
- Disadvantages include the contraindication in severe renal dysfunction (Cr Cl < 30mL/min) and the needle size.
- **Dulaglutide (Trulicity)** is a once weekly GLP1RA with a small needle size. It does not require dosing adjustment for patients with renal dysfunction. Patients currently receiving Trulicity at the MTFs can remain on therapy.
- **Albiglutide (Tanzeum) supply will be exhausted by August 2018.** Current MTF patients on Tanzeum must be transitioned over to Bydureon/Bydureon BCise or Trulicity prior to the market discontinuation. **Existing MTF Tanzeum supply can be depleted, but there should be no new patient starts on Tanzeum.**
- **Liraglutide (Victoza) is one of the most expensive GLP1RAs for the DoD.** MTFs are strongly urged to review the patient profiles for patients currently on Victoza to consider changing therapy to Bydureon/Bydureon BCise or Trulicity if clinically appropriate, e.g., they have failed to achieve target A1C levels with Bydureon/Bydureon BCise and Trulicity. **There are still a significant number of MTF patients on Victoza; if these patients remain on Victoza, the excess costs to DoD will be approximately \$9 million annually at the MTFs alone.**
- Liraglutide is also available for weight loss in a higher dose formulation (Saxenda); Victoza should only be used in patients with diabetes, and not for weight loss. Quantity limits now apply to Victoza., to discourage use solely for weight loss.
- **Semaglutide (Ozempic)** is the 4th once weekly GLP1RA available in a pre-filled pen with a small needle size.
 - Overall, differences in A1c between the GLP1RAs are not clinically relevant, however a clinically significant difference was shown in one open-label, active comparator study (SUSTAIN-3) between semaglutide and exenatide. Semaglutide lowered A1c by 1.5% from baseline compared to 0.9% with exenatide. Limitations to the SUSTAIN-3 study include the open label, active comparator design; it was not designed to show superiority.
 - In the open-label, active comparator SUSTAIN-7 study, semaglutide was statistically superior to dulaglutide (Trulicity) in glycemic control, as it reduced A1c by 1.5-1.8% from baseline compared to 1.1-1.4% with dulaglutide. However, the differences in change in A1c between semaglutide and dulaglutide were not considered clinically relevant, as the change in A1c was less than 0.5%.

Safety

- The reported incidence of hypoglycemia with GLP1RAs is low; however, the incidence is higher when a GLP1RA is used with a sulfonylurea.
- The incidence of nausea varies based on the GLP1RA dosing, with higher doses resulting in more nausea. Bydureon/Bydureon BCise has the lowest incidence of nausea (14%) compared to Trulicity (12-21%), Ozempic (16-20%), Victoza (23%), Adlyxin (29%), and Byetta (35%).
- Adverse events are likely to occur early on in therapy, and then subside with continued use.

Cardiovascular Outcomes Trials (CVOTs)

- There are 4 completed CVOTs including LEADER with liraglutide, SUSTAIN-6 with semaglutide, EXSCEL with exenatide, and ELIXA with lixisenatide. The REWIND trial with dulaglutide and HARMONY-OUTCOME with albiglutide are ongoing. These trials evaluated time to major adverse cardiovascular events with the GLP1RAs, including CV mortality, non-fatal myocardial infarction, and stroke.
- Liraglutide has an additional indication to reduce CV risk in patients with established CV disease, based on the LEADER trial. However the hazard ratios and confidence intervals of the composite endpoints overlap for LEADER, ELIXA, and EXSCEL. Additionally, given the differences in patient populations (baseline A1c, duration of diabetes, percent of patients with established CV disease, etc.) in the CVOTs, it is difficult to directly compare one GLP1RA to another in terms of CV benefit. Also note that the LEADER results in U.S. patients did not reach statistical significance, compared to patients outside the U.S.
- **It is clinically appropriate to re-evaluate the need for continued GLP1RA treatment on an annual basis.** If A1c response is not optimal, consider insulin therapy. If CV risk reduction is needed in a diabetic patient, consider other drugs with CVOT data, including aspirin, statins, or the SGLT2 inhibitor empagliflozin (Jardiance).

- In all four CVOTs to date, the association of GLP1RAs use with retinopathy has been a concern; however this was a secondary outcome and the studies have not been powered to adequately assess worsening retinopathy. Additional trials are needed to definitively determine the long term effects of GLP1RAs on diabetic retinopathy.

Prior Authorization (PA) Criteria for GLP1RAs

- All new users of any GLP1RA must first try metformin before receiving a GLP1RA unless contraindications to metformin exist.
- Manual PA criteria:** Bydureon/BCise, Trulicity, Byetta, Victoza, Adlyxin, or Ozempic is approved (e.g., trial of metformin is NOT required) if:
 - The patient has a confirmed diagnosis of Type 2 diabetes mellitus
 - The patient has experienced any of the following issues on metformin:
 - impaired renal function precluding treatment with metformin
 - history of lactic acidosis
 - The patient has had inadequate response to metformin
 - The patient has a contraindication to metformin
- Additionally, Bydureon/BCise and Trulicity are the preferred agents in the GLP1RA subclass. New and current users of Byetta, Victoza, Adlyxin, and Ozempic must try Bydureon/BCise and Trulicity first.**
- Manual PA Criteria:** In addition to the above criteria regarding metformin, the following PA criteria would apply specifically to new and current users of Byetta, Victoza, Adlyxin and Ozempic:
 - The patient has had inadequate response with Bydureon/BCise and Trulicity

References

- DoD P&T Committee minutes: <http://www.health.mil/PandT>
- Current/future drug classes under review by the DoD P&T Committee: <http://www.health.mil/PandT> (scroll down to DoD P&T Committee Meeting Schedule)
- TRICARE Formulary Search Tool: <http://www.health.mil/formulary>
- Prior Authorization/Medical Necessity forms: See Formulary Search Tool above.
- Formulary Management Documents (including this one) available at: <http://www.health.mil/DoDPTResources>
- Point of contact for additional information: dha.jbsa.pharmacy.list.poduf@mail.mil
- ADA Guidelines. *Diabetes Care* 2018;41(Suppl. 1):S73-S85.
- AACE Guidelines. *Endocr Pract.* 2015;21(4):e1-10.

GLP1RA Price Comparison at MTF	
Drug	MTF Cost (February 2018)
Basic Core Formulary Step-Preferred	
Exenatide Q Week (Bydureon/Bydureon BCise)	\$ = Most Cost-Effective
Uniform Formulary Step-Preferred	
Dulaglutide (Trulicity)	\$ = Most Cost-Effective
Non-Formulary Non-Step-Preferred	
Exenatide BID (Byetta)	\$\$\$ = Less Cost-Effective
Liraglutide (Victoza)	\$\$\$\$ = Least Cost-Effective
Lixisenatide (Adlyxin)	\$\$\$\$ = Least Cost-Effective
Semaglutide (Ozempic)	\$\$\$\$ = Least Cost-Effective
Legend: \$ = "Most Cost-Effective" represents Rx's with the <u>lowest cost</u> and/or best clinical efficacy \$\$ = "Less Cost-Effective" represents <u>higher cost</u> Rx's with similar clinical efficacy \$\$\$ = "Less Cost-Effective" represents <u>next higher cost</u> Rx's with similar clinical efficacy \$\$\$\$ = "Least Cost-Effective" represents Rx's with the <u>highest cost</u> with similar clinical efficacy	