

# Long-Term Care Updates

May 2024

## Management of GLP-1 Receptor Agonist Therapy Interruption



By Ariel Dunn-Evanczuk, PharmD Candidate

### Introduction

There have been numerous drug shortages since early 2022 affecting the availability of long-acting glucagon-like peptide 1 (GLP-1) receptor agonists.<sup>1</sup> This newsletter will address the GLP-1/GIP agonist, tirzepatide, alongside other GLP-1s. Guidance for clinicians and patients has been lacking on how to handle these shortages with respect to interruptions in therapy. Patients who have been maintained on a weekly dose, may go for extended periods of time without medication.

This newsletter will consider the appropriate approaches to restart patients on GLP-1 therapy after various interruption times.

### Evidence Review

Package inserts include guidance only on single missed doses, dependent on product (exception of Wegovy). Tirzepatide (Mounjaro and Zepbound) should be given as soon as possible if missed within 96 hours or skipped until the next regular dose if greater than 96 hours.<sup>2,3</sup> Dulaglutide (Trulicity) should be administered if there is at least 72 hours before the next scheduled dose.<sup>4</sup> Semaglutide (Wegovy) should be administered until 48 hours prior to the next dose. If more than two doses of Wegovy are missed, clinician judgment should be used to determine if the patient should be restarted at 0.25 mg weekly and re-escalated.<sup>5</sup> Semaglutide (Ozempic) should be administered within 5 days of the missed dose or skipped until the next weekly dose.<sup>6</sup> Exenatide (Bydureon) should be administered if the next dose is at least 3 days later.<sup>7</sup> In the case of all products, patients should resume regularly scheduled dosing on their next dose due date.<sup>2,3,4,5,6,7</sup>

Creighton University Center for Drug Information & Evidence-Based Practice  
Drug Information Consultation Service

Monday through Friday; 7:30am-3:30pm Central  
1-800-561-3728; *Voicemail service is available after-hours*

Submit your questions [HERE](#).

Due to the product shortage since early 2022, the American Diabetes Association issued a special report on strategies for addressing product unavailability in the summer of 2023. Their recommendations are as follow:<sup>9</sup>

Agent	Last Dose Administered	Recommendation(s) for Resuming Therapy
Dulaglutide	1.5 mg once weekly	<ul style="list-style-type: none"> <li>Resume at 1.5 mg weekly</li> <li>Expect comparable tolerability to that experienced prior to dose interruption</li> </ul>
	3 or 4.5 mg once weekly	<ul style="list-style-type: none"> <li>Use best judgment if <math>\geq 3</math> doses are missed</li> <li>It is unknown whether tolerance to GI adverse events will remain if initiated at the higher dose after <math>\geq 3</math> missed</li> <li>Decision can be informed by patient's prior GI tolerability</li> <li>In consideration of the above, clinicians may consider reinitiating at 1.5 mg once weekly</li> </ul>
Injectable semaglutide	1 mg once weekly	<ul style="list-style-type: none"> <li>If <math>\leq 2</math> doses are missed, reinitiate at 1 mg weekly</li> <li>If 3-4 doses are missed, reinitiate at 0.5 mg weekly</li> <li>If <math>\geq 5</math> doses are missed, reinitiate at 0.25 mg weekly</li> </ul>
Tirzepatide	$\geq 5$ mg once weekly	<ul style="list-style-type: none"> <li>If <math>\leq 2</math> doses are missed, reinitiate at the same dose</li> <li>If <math>\geq 3</math> doses are missed, reinitiate at 5 mg weekly</li> </ul>

Other recommendations from the special report include methods for altering the dose of available products and switching of products. Semaglutide is available as a dialable dose pen, which allows for multiple doses from a single product. This method is not supported by the manufacturer. Dulaglutide and tirzepatide are only available as single, unadjustable dose pens, however 0.75 mg twice weekly could replace 1.5 mg weekly dosing. This dosing schedule was used in a phase 2 study for dulaglutide, but was not studied in tirzepatide.<sup>9</sup> Dosing equivalents for switching products follow:<sup>9</sup>

Agent	Comparative Doses						
Exenatide XR		2 mg					
Dulaglutide	0.75 mg	1.5 mg	3 mg	4.5 mg			
Semaglutide SC	0.25 mg	0.5 mg		1 mg	2 mg		
Tirzepatide		2.5 mg			5 mg	7.5 mg	10 mg

These alternative recommendations are further supported by an article in Pharmacist's Letter, published in February 2024. This article suggests stepping patients to a lower dose temporarily or using an alternate product.<sup>8</sup>

A 2021 study by Frias et al., comparing tirzepatide to semaglutide included temporary discontinuation as part of the study protocol. For tirzepatide, if  $\leq 2$  consecutive doses were missed, it was restarted at the same dose, if well tolerated prior to discontinuation. If  $\geq 3$  consecutive doses were missed, it was restarted at 5 mg irrespective of the previous dose and subsequently escalated. For semaglutide, if  $\leq 2$  doses were missed, it was restarted at 1 mg. If 3-4 consecutive doses were missed, patients were given 4 weeks on 0.5 mg before escalation. If  $\geq 5$  doses were missed, a full dose escalation was performed, starting at 0.25 mg weekly.<sup>10</sup>

Eli Lilly provides some guidance on dulaglutide (Trulicity) missed doses. Only 0.75 mg and 1.5 mg doses were studied for initial dosing, therefore the company does not have recommendations on starting at higher doses after prolonged interruptions. Doses of 0.75 mg or 1.5 mg can be resumed at any time after interruption. Clinician judgment is recommended on restarting patients at higher doses after 3 or more missed doses. Dose escalation is likely to help reduce expected GI side effects.<sup>11</sup>

### Conclusion

Product availability issues have caused interruption of therapy for patients utilizing GLP-1 receptor agonists. Little information is provided on how to restart patients after prolonged missed therapy. In the case of tirzepatide (Mounjaro), the best recommendation comes from the American Diabetes Association. Patients missing 2 or fewer consecutive doses should be resumed at their former dose. Patients missing 3 or more doses should be restarted at 5 mg weekly and then be dose escalated to their former dose.<sup>9</sup> Because tirzepatide is a unique product, both a GLP-1 and GIP agonist, switching products may be less desirable. Depending on product availability, lower dose products given twice weekly to equal the desired dose may be an acceptable alternative, though this is not supported by the manufacturer.<sup>9</sup>

### References

1. *FDA drug shortages*. FDA Drug Shortages. 29 March, 2024. <https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>
2. Tirzepatide (Mounjaro) [package insert]. Indianapolis, IN: Lilly USA, LLC; 2022.
3. Tirzepatide (Zepbound) [package insert]. Indianapolis, IN: Lilly USA, LLC; 2023.
4. Dulaglutide (Trulicity) [package insert]. Indianapolis, IN: Lilly USA, LLC; 2022. .
5. Semaglutide (Wegovy) [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; 2023
6. Semaglutide (Ozempic) [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; 2023
7. Exenatide (Bydureon) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023.
8. Therapeutic Research Center. (2024, February). *Help navigate common hurdles with GLP-1 agonists*. Pharmacist's Letter. <https://pharmacist.therapeuticresearch.com/Content/Articles/PL/2024/Feb/Help-Navigate-Common-Hurdles-With-GLP-1-Agonists> .
9. Whitley HP, Trujillo JM, Neumiller JJ. Special Report: Potential Strategies for Addressing GLP-1 and Dual GLP 1/GIP Receptor Agonist Shortages. *Clin Diabetes*. 2023 Summer;41(3):467-473.
10. Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med* 2021;385:503–515.
11. Eli Lilly and Company . If a patient stopped Trulicity (dulaglutide) treatment for a few weeks, should they restart on their previous dose or re-escalate from the 0.75 mg dose? Available from <https://www.lillymedical.com/en-us/answers/if-a-patient-stopped-trulicity-dulaglutide-treatment-for-a-few-weeks-should-they-restart-on-their-previous-dose-or-re-escalate-from-the-0-75-mg-dose-152166?hcpToken=A12DSa08bhrd123gg8&channel=AE>. Accessed 2 April 2024.