Compounded GLP 1 and Dual GIP/GLP 1 Receptor Agonists: A Statement from the American Diabetes Association

Joshua J. Neumiller,[1] Mandeep Bajaj,[2] Raveendhara R. Bannuru,[3] Rozalina G. McCoy,[4] Elizabeth J. Pekas,[3] Alissa R. Segal,[5] and Nuha A. ElSayed[3,6]

https://doi.org/10.2337/dci24-0091

The use of glucagon-like peptide 1 receptor agonist (GLP-1 RA) and dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA (GIP/GLP-1 RA) classes has increased substantially over the past several years for treating type 2 diabetes and obesity. Increased demand for these pharmacotherapies has resulted in temporary product shortages for both GLP-1 RA and dual GIP/GLP-1 RA medications. These shortages, in part, have led to entities producing and marketing compounded formulations that bypass regulatory measures, raising safety, quality, and efficacy concerns. Even as shortages resolve, compounded GLP-1 RA and GIP/GLP-1 RA products continue to be heavily marketed to people with diabetes and obesity. The purpose of this statement by the American Diabetes Association is to guide health care professionals and people with diabetes and/or obesity in these circumstances of medication unavailability to promote optimal care and medication use safety.

Clinical demand for agents from the glucagon-like peptide-1 receptor agonist (GLP-1 RA) and dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA (dual GIP/GLP-1 RA) classes has increased dramatically in recent years (1). These medications are recommended by the American Diabetes Association (ADA) for use in people with type 2 diabetes to *1*) mitigate cardiovascular and kidney disease risks in high-risk individuals and *2*) achieve and maintain glycemic and weight management goals (2). The U.S. Food and Drug Administration (FDA) approved several incretin-based agents as weight loss therapies, which fueled a demand temporarily exceeding the available supply. Resulting intermittent shortages prompted multiple entities to produce and market compounded formulations of these therapies directly to consumers (3), in some instances bypassing the involvement of the individual's usual health care team. While compounded medications—medication formulations locally produced and customized to meet individualized clinical needs—play an import role within the health care system, specific concerns have emerged surrounding the recent widespread availability and use of non-FDA-approved incretin-based products. Given concerns about the safety, quality, and effectiveness, the ADA is issuing the following guidance on the use of non-FDA-approved compounded products.

GUIDANCE STATEMENTS

- Non-FDA-approved compounded incretin products are not recommended for use due to uncertainty about their content and resulting concerns about safety, quality, and effectiveness.

[1]Department of Pharmacotherapy, Washington State University, Spokane, WA
[2]Department of Medicine, Baylor College of Medicine, Houston, TX
[3]American Diabetes Association, Arlington, VA
[4]Division of Endocrinology, Diabetes, and Nutrition, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD
[5]Massachusetts College of Pharmacy and Health Sciences, Boston, MA
[6]Harvard Medical School, Boston, MA

Corresponding author: Nuha A. ElSayed, nelsayed@diabetes.org

Received 15 October 2024 and accepted 4 November 2024

This American Diabetes Association (ADA) statement was reviewed and approved by the ADA Professional Practice Committee in October 2024.

An ADA statement is an official ADA point of view or position that does not contain clinical practice recommendations and may be issued on advocacy, policy, economic, or medical issues related to diabetes. ADA statements undergo a formal review process, including external peer review and review by the appropriate ADA national committee, ADA clinical leadership, ADA scientific team, and, as warranted, the ADA Board of Directors.

- If an incretin medication is unavailable (e.g., in shortage), switching to a different FDA-approved medication is recommended as clinically appropriate to achieve and maintain individualized glucose-lowering, weight management, and/or cardiovascular and kidney risk reduction goals.
- Upon resolution of incretin product unavailability, reassess the appropriateness of resuming the original FDA-approved incretin medication.

The ADA recommends against using non-FDA-approved compounded GLP-1 and dual GIP/GLP-1 RA products due to safety, quality, and effectiveness concerns and uncertainty about their content. Compounded products are not FDA-approved (4) and do not undergo FDA review for safety, quality, or effectiveness standards (5). As a result, these products may present elevated risks to individuals.

Increased demand for GLP-1 RA and dual GIP/GLP-1 RA therapies resulted in shortages of drug products and/or delivery devices and culminated in the listing of several agents on the FDA shortage list. The FDA allows for compounding copies (i.e., products intended to be an exact duplicate) of FDA-approved products that are listed on the FDA shortage list (only) to facilitate continuity of treatment and uninterrupted access to prescribed pharmacotherapies (6). Human drug compounding is regulated per sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (7). Section 503A applies to human drug compounding by a licensed pharmacist within a state-licensed pharmacy or federal facility or by a licensed physician. Section 503B provides guidance for human drug compounding by outsourcing compounding facilities (7). Compounding under section 503A allows the production of relatively small quantities of compounded products, with 503A compounding facilities largely regulated by state boards of pharmacy. In contrast, 503B facilities are regulated by the FDA and are permitted to manufacture large quantities of compounded products, but only while these products are actively listed on the FDA shortage list (6).

While the FD&C Act allows for compounding of GLP-1 RA and dual GIP/GLP-1 RA therapies by licensed and approved facilities while under shortage (and, specifically, listed on the FDA drug shortage list), several concerns exist regarding the safety, quality, and effectiveness of such non-FDA-approved products (Table 1).

Compounded GLP-1 RA and Dual GIP/GLP-1 RA Therapies Are Not Identical to the FDA-Approved Products. Compounding a copy of an FDA-approved product would ideally follow a U.S. Pharmacopoeia (USP) monograph or other standard to ensure product quality. However, USP monographs for most GLP-1 RA and the dual GIP/GLP-1 RA therapies are currently unavailable to guide standard compounding (8). USP monographs detail quality expectations for a medicine, including its identity, strength, purity, and performance (9). USP monographs also provide product testing recommendations for validation of a product's strength, purity, and performance (9). USP generally begins developing product monographs a few years prior to patent expiration (9); thus, USP monographs are not currently available for products like semaglutide or tirzepatide. Reports by the FDA have noted several ways compounded incretin-based therapies encountered in the marketplace may differ from FDA-approved products. According to the FDA, some compounded products have incorporated additional ingredients (e.g., vitamin B12 or vitamin B6) in the compounded GLP-1 RA formulation. Added ingredients within compounded formulations inherently change the composition of the compounded product relative to its FDA-approved reference product. Because compounded products are not subject to bioequivalence testing, as is required for FDA-approved generic medications, the impact of added ingredients on the pharmacokinetics, pharmacodynamics, efficacy, and safety of the medication is unknown (10). The FDA has also received early reports of compounders using salt forms of semaglutide (e.g., semaglutide sodium or semaglutide acetate) as a substitute for the semaglutide base used in the FDA-approved products (5). Salt forms of a small molecule are not chemically identical to the non-salt form of that molecule, which may similarly result in clinically meaningful differences in the effectiveness and safety of the compounded product compared with the FDA-approved product.

Compounded GLP-1 RA and Dual GIP/GLP-1 RA Products Have Been Associated With Clinically Important Dosing Errors and Adverse Events. The FDA issued an alert in July 2024 detailing dosing errors associated with compounded semaglutide products (11,12). Several factors were identified as potentially contributing to dosing errors and associated adverse events (Table 2). While FDA-approved products are available only in prefilled pens and single-dose vials that deliver standardized dosing in milligrams, compounded products may be compounded in varying concentrations (even from the same compounder) and dispensed in variable packaging, including multidose vials or prefilled syringes (11,13). The FDA alert details reported administration errors at doses 5- to 20-fold higher than intended. According to the report, many individuals lacked experience with self-injection, were inexperienced with drawing medication from a vial into a syringe, and/or experienced confusion regarding the units of measurement (such as milliliters, milligrams, and/or "units") listed on product labels, administration instructions, and/or provided syringes (11). Some of the reported cases resulted in adverse events, including gastrointestinal effects, fainting, headache, dehydration, acute pancreatitis, and gallstones—in some instances requiring hospitalization (11,12).

Table 1—Key concerns regarding the safety, quality, and effectiveness of non-FDA-approved compounded products

- Compounded GLP-1 RA and dual GIP/GLP-1 RA products are not identical to the FDA-approved products. USP monographs for GLP-1 RA and dual GIP/GLP-1 RA therapies are currently not available to guide standard compounding. Ideally, compounding a copy of an FDA-approved product would follow a USP monograph or other standard to ensure product quality.
- Compounded GLP-1 RA and dual GIP/GLP-1 RA products have been associated with clinically important dosing errors and adverse events.
- More concerning to individuals' safety are counterfeit products that have made their way into the U.S. drug supply chain and those advertised online and by unregulated sources.

Table 2—Factors that may contribute to dosing errors with compounded GLP-1 RA and dual GIP/GLP-1 RA products

• Compounded products may be dispensed in varying concentrations (even from the same compounding pharmacy or facility).
• Compounded products are generally not dispensed in prefilled pens or single-dose vials that deliver standardized doses. Products may be dispensed to individuals in multidose vials or prefilled syringes, increasing the likelihood of administration errors.
• Individuals receiving these products from online distributors or other sources may not receive appropriate education on self-injection and/or appropriate preparation of the desired/prescribed dose.
• Confusion may occur regarding the variable units of measurement (such as milliliters, milligrams, and/or "units") listed on product labels, administration instructions, and/or provided syringes for administration.

The information in this table is based on information from the FDA (11).

More Concerning to Individuals' Safety Are the Counterfeit Products That Have Made Their Way Into the U.S. Drug Supply Chain and Those Advertised Online and by Unregulated Sources. Counterfeit compounded GLP-1 RA and dual GIP/GLP-1 RA products pose significant risks. Determining whether online suppliers of compounded products are reputable or predatory can be difficult for individuals and health care professionals. Even reputable and trusted suppliers and sources may unknowingly market a counterfeit product. A recently published study highlighted important safety and purity concerns related to online distributors of semaglutide products, reporting online vendors that collected payment and did not provide product, issues with product purity and concentrations, and even concerns about product contamination (14). Clinicians have further reported instances of people presenting to the clinic with compounded GLP-1 RA and dual GIP/GLP-1 RA dosage forms not available for the FDA-approved products (e.g., oral and sublingual products) and even compounded incretin therapies not yet approved by the FDA (e.g., retatrutide). The increasing availability of such products poses important concerns about product safety, quality, and effectiveness (15).

Data on the adverse consequences of compounded GLP-1 RA and dual GIP/GLP-1 RA product use are only beginning to emerge. The actual scope of the problem is likely much higher, as often the responsibility of reporting adverse events associated with compounded products falls on the individual experiencing these events rather than a member of their health care team, and many individuals and health care professionals may lack knowledge of the appropriate reporting process. Even if known, the reporting process can be cumbersome, thereby hindering timely and complete reporting. Other non-FDA-approved compounded products have been linked to patient harm, including death (16,17), but none of these products were as widely used and broadly marketed as compounded GLP-1 RA and dual GIP/GLP-1 RA products. Individuals and health care professionals should report all potential or experienced adverse consequences using the FDA's MedWatch reporting system to ensure accurate accounting of events and provide the appropriate authorities with information for further investigation into the events (18).

Given the substantive concerns about safety and effectiveness of non-FDA-approved compounded products, when a glucose-lowering or weight management medication is unavailable (e.g., in shortage), the ADA recommends switching to a different FDA-approved medication as clinically appropriate to achieve and maintain individualized treatment goals. This may include switching to an alternative agent within a therapeutic class or using an agent from another therapeutic class, depending on individualized therapeutic needs and goals (19). Upon resolution of product unavailability, it is recommended that the health care professional reassess whether to resume the original FDA-approved medication or continue the FDA-approved treatment used in the interim to bridge care based on the individual's current care needs, preferences, and priorities.

Resources and Advice for Professionals, Caregivers, and Individuals Considering Use of a Compounded GLP-1 RA or Dual GIP/GLP-1 RA Product. While the ADA recommends against using non-FDA-approved compounded products, the ADA also recognizes that individuals and clinicians may still elect to use or recommend compounded products for financial or other reasons. Accordingly, we offer the following resources for professionals, caregivers, and individuals. The ADA recognizes that the information provided below may not apply to every situation because individuals with diabetes and/or obesity will have varying members of their existing care team and may or may not have used a GLP-1 RA or dual GIP/GLP-1 RA product in the past. For clinicians recommending the use of a compounded product, it is recommended that they or a designee work with the individual to ensure the product is purchased from a reputable source and that they understand how to use and administer the product safely.

If electing to use a compounded product, individuals are encouraged to do the following.

- Individuals should discuss use of the compounded product with their usual health care professional before purchasing a compounded product.
  - Health care professionals not associated with the individual's usual care team (e.g., compounding pharmacists or staff physicians with online retailers) will not have access to their medical or family history or current medications that would allow for a thorough safety assessment and may not be involved in ongoing necessary safety monitoring after initiating the treatment.
- Individuals should seek and receive guidance about appropriate dosing and administration from the compounding pharmacy/pharmacist to minimize the risk of dosing errors and associated adverse events.
  - If individuals have never injected/administered a product using the method purchased, individuals should receive education on proper administration of the product from the individual/entity dispensing the compounded product.
- Individuals should not use products that do not have a label noting the specific dosage (including units) and the exact contents of the product.

Table 3—Key warning signs that an online pharmacy or distributor of compounded products may be unsafe

• A valid prescription is not required.
• The pharmacy/distributor is not licensed in the U.S. or by a state board of pharmacy.
• There is no licensed pharmacist on staff available to answer questions.
• The product received looks different (e.g., the solution is a different color, is cloudy, or contains particulate) than what the individual received at a local pharmacy (for those previously taking an FDA-approved product) or arrives in packaging that is broken, damaged, labeled in a foreign language, has no expiration date, or is expired.
• Deep discounts or prices art offered that are seemingly too good to be true.
• Individuals are charged for products never ordered or received.
• The online pharmacy or distributor does not provide clearly written information about how they protect personal or financial information, or they sell personal or financial information to a third party.

The information in this table is based on information from the FDA (21).

  - Individuals should carefully examine product appearance (e.g., labeling and clarity of the drug product) and contact the compounding pharmacist or the clinician prescribing the compounded product with questions or concerns prior to use (Table 3) (20).

- Individuals should verify that the compounding pharmacy is registered with the FDA (503B compounding facilities) or licensed with an applicable state board of pharmacy (503A compounding facilities).
  - Facilities registered as human drug compounding outsourcing facilities under section 503b of the FD&C Act: https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilities
  - Directory of state-licensed online pharmacies by state: https://www.fda.gov/drugs/besaferx-your-source-online-pharmacy-information/locate-state-licensed-online-pharmacy
- Individuals should avoid purchasing compounded products from online sources that are not registered with the FDA. Individuals should be aware of key warning signs that may indicate an online pharmacy or distributor is unsafe (Table 3) (21).
- Any adverse events or medication errors associated with the use of non-FDA-approved compounded products should be reported to MedWatch using the following link: https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program.
  - Additional information on MedWatch reporting by health professionals: https://www.fda.gov/safety/reporting-serious-problems-fda/reporting-health-professionals#:~:text=Call%201%2D800%2DFDA%2D,do%20not%20send%20instruction%20pages
  - A toll-free line is also available to ask questions and/or report issues to FDA: 1-800-332-1088.
- Individuals should notify their usual care team when they start or stop a compounded product, as this may necessitate changes to their overall diabetes management plan.

As the use of GLP-1 RAs and dual GIP/GLP-1 RA products continues to rise, intermittent shortages are likely to persist. Although compounded medications play a critical role in the health care system, there are numerous concerns regarding the availability and use of non-FDA-approved versions of these products. Due to the potential issues about safety, quality, and effectiveness of these products, the ADA urges health care professionals to consider switching individuals to a different FDA-approved medication to achieve and maintain individualized glucose-lowering, weight management, and/or cardiovascular and kidney risk reduction goals. Additionally, regulatory authorities should continue prioritizing safety and enforcement of compounding standards to ensure safe and reliable options during critical drug shortages. Situations of shortage for any reason should be evaluated on an ongoing basis, and the appropriateness of resuming the FDA-approved medication should be considered when appropriate. If health care professionals, caregivers, and/or individuals are considering use of compounded GLP-1 RA or dual GIP/GLP-1 RA products, the ADA offers the present guidance to be considered in conjunction with clinical judgement and individual preferences.

Acknowledgments. The authors thank Dr. David A. D'Alessio (Duke University Division of Endocrinology), Dr. Bruce Ruck (Rutgers New Jersey Medical School and New Jersey Poison Information and Education System), and Dr. Masha Yemets (Marland Poison Control Center).

Funding. This statement was funded by ADA general revenue. No other entity, including industry, provided support for this statement.

Duality of Interest. J.J.N. is a consultant for Proteomics International. M.B. has received research support from the ADA. R.G.M. has received research support, speaking honoraria, and travel funds from the ADA. A.R.S. has received support for reviewing of continuing medical education materials and infographics from the ADA. No other potential conflicts of interest relevant to this article were reported.

Handling Editors. The journal editors responsible for overseeing the review of the manuscript were Elizabeth Selvin and Vanita R. Aroda.

References

1. Watanabe JH, Kwon J, Nan B, Reikes A. Trends in glucagon-like peptide 1 receptor agonist use, 2014 to 2022. J Am Pharm Assoc (2003) 2024; 64:133–138
2. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: *Standards of Care in Diabetes—2024*. Diabetes Care 2024;47:S158–S178
3. U.S. Food & Drug Administration. Medications Containing Semaglutide Marketed for Type 2 Diabetes or Weight Loss. Accessed 1 August 2024. Available from https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/medications-containing-semaglutide-marketed-type-2-diabetes-or-weight-loss
4. U.S. Food & Drug Administration. Consumer and Health Care Professional Information. Accessed 1 August 2024. Available from https://www.fda.gov/drugs/human-drug-compounding/consumer-and-health-care-professional-information
5. U.S. Food & Drug Administration. Compounding and the FDA: Questions and Answers. Accessed 1 August 2024. Available from https://www.fda.gov/drugs/human-drug-compounding/compounding-and-fda-questions-and-answers
6. U.S. Food & Drug Administration. Drug Compounding and Drug Shortages. Accessed 1 August 2024. Available from https://www.fda.gov/drugs/human-drug-compounding/drug-compounding-and-drug-shortages
7. U.S. Food & Drug Administration. FD&C Act Provisions that Apply to Human Drug Compounding. Accessed 1 August 2024. Available from https://www.fda.gov/drugs/human-drug-compounding/fdc-act-provisions-apply-human-drug-compounding

8. U.S. Pharmacopeia (USP). USP Reference Standards. Accessed 3 October 2024. Available from https://www.usp.org/reference-standards
9. U.S. Pharmacopeia (USP). An Overview of USP Monographs. Accessed 29 September 2024. Available from https://www.usp.org/about/public-policy/overview-of-monographs
10. Gudeman J, Jozwiakowski M, Chollet J, Randell M. Potential risks of pharmacy compounding. Drugs R D 2013;13:1–8
11. U.S. Food & Drug Administration. FDA alerts health care providers, compounders and patients of dosing errors associated with compounded injectable semaglutide products. Accessed 1 August 2024. Available from https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-providers-compounders-and-patients-dosing-errors-associated-compounded
12. Lambson JE, Flegal SC, Johnson AR. Administration errors of compounded semaglutide reported to a poison control center-Case series. J Am Pharm Assoc (2003) 2023;63:1643–1645
13. Lilly releases Zepbound® (tirzepatide) single-dose vials, expanding supply and access for adults living with obesity. Accessed 3 September 2024. Available from https://investor.lilly.com/news-releases/news-release-details/lilly-releases-zepboundr-tirzepatide-single-dose-vials-expanding
14. Ashraf AR, Mackey TK, Schmidt J, et al. Safety and risk assessment of no-prescription online semaglutide purchases. JAMA Netw Open 2024;7:e2428280
15. U.S. Food & Drug Administration. FDA warns consumers not to use counterfeit Ozempic (semaglutide) found in U.S. drug supply chain. Accessed 1 August 2024. Available from https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-consumers-not-use-counterfeit-ozempic-semaglutide-found-us-drug-supply-chain
16. The PEW Charitable Trusts. U.S. Illnesses and Deaths Associated With Compounded or Repackaged Medications, 2001-19. Accessed 23 August 2024. Available from https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2020/us-illnesses-and-deaths-associated-with-compounded-or-repackaged-medications-2001-19
17. Centers for Disease Control and Prevention. Multistate outbreak of fungal infection associated with injection of methylprednisolone acetate solution from a single compounding pharmacy - United States, 2012. MMWR Morb Mortal Wkly Rep 2012;61:839–842
18. U.S. Food & Drug Administration. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. Accessed 23 August 2024. Available from https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program
19. 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;41:467–473
20. U.S. Food & Drug Administration. Counterfeit Medicine. Accessed 1 August 2024. Available from https://www.fda.gov/drugs/buying-using-medicine-safely/counterfeit-medicine
21. U.S. Food & Drug Administration. Considering an Online Pharmacy? Accessed 1 August 2024. Available from https://www.fda.gov/drugs/besaferx-your-source-online-pharmacy-information/considering-online-pharmacy