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ISMP
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Community/Ambulatory Care
ISMP Medication Safety Alert!®
Educating the Healthcare Community About Safe Medication Practices

Increased demand and shortages of GLP-1 receptor agonists contributes to patient harm

Problem: Many people struggle to maintain a healthy body weight. In fact, the Centers for Disease Control and Prevention (CDC) has estimated that more than 40% of adults in the United States are obese.[1] Even though they may try new diets or exercise programs, many people struggle to adhere to these lifestyle changes to maintain any weight loss. To help with their efforts, some people have turned to prescription medications, but, until more recently approved drugs, most of these therapies did not always prove to be significantly effective.

Glucagon-like peptide-1 (GLP-1) receptor agonists (e.g., semaglutide [**OZEMPIC**], liraglutide [**VICTOZA**]) were originally developed and approved to treat patients with type 2 diabetes by improving glycemic control, along with diet and exercise. They are available primarily in prefilled pen devices; however, **MOUNJARO** (tirzepatide) is also approved to be manufactured in single-dose vials, and **RYBELSUS** (semaglutide) is an oral tablet. Clinicians and researchers observed that these medications also helped patients lose weight. So, the pharmaceutical manufacturers developed products (e.g., **WEGOVY** [semaglutide], **SAXENDA** [liraglutide], **ZEPBOUND** [tirzepatide]) indicated specifically for chronic weight management. In conjunction with lifestyle changes (e.g., diet and exercise), these medications have been found to help patients achieve clinically significant weight loss.[2] With this news and the power of social media, the interest in these medications has exploded. At one point semaglutide was known as the "hottest drug in Hollywood." All of this interest led to a dramatic increase in the demand for the products and has resulted in long-lasting drug shortages for semaglutide (since March 2022), liraglutide (since July 2023), and tirzepatide (since December 2022).[3,4] In addition, Novo Nordisk, the manufacturer of Ozempic, discontinued Ozempic 0.25 mg and 0.5 mg dose strengths in the 2 mg/1.5 mL presentations further impacting the availability of these drugs.

Errors and Adverse Effects with Compounded Weight-Loss Drugs

Due to these drug shortages, compounding pharmacies and others have been preparing compounded versions of the drugs. However, both the US Food and Drug Administration (FDA) and America's Poison Centers have reported receiving cases of patients experiencing medication errors and adverse events following the use of compounded semaglutide products.[5,6] The Utah Poison Control Center described three cases of adverse events. The patients had received the medications from compounding pharmacies and an aesthetic spa. Two patients administered 10 times the amount of drug to themselves. One of the patients reported receiving a vial of medication from the compounding pharmacy. Another one of the patients reported that their medication had been co-formulated with catecholamine (synthetic vitamin B_{12}). All three patients experienced symptoms such as nausea, vomiting, and abdominal pain. One patient required treatment in an emergency department (ED). The Poison Control Center noted that the patients had not received counseling from a pharmacist.

ISMP has also been receiving reports of patients experiencing medication errors and adverse events after receiving compounded semaglutide and tirzepatide. Some of the products were not labeled. In one case, a hospital reported having three patients requiring admission to the intensive care unit (ICU) in less than a week due to hypoglycemia from compounded semaglutide. The patients reported receiving multiple pens without a prescription from people they identified as "nurses" in a hotel room or a gathering akin to a "Botox party."

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Safe drug administration during fasting. Fasting is practiced by several cultures around the world. For example, during Ramadan, which begins on the evening of March 10 and ends on April 9 this year, Muslims who fast refrain from certain activities, including eating and drinking, from dawn until sunset. While practices may allow for exemptions from fasting, including if it is detrimental to one's health (e.g., diabetes, pregnancy, immunocompromised condition, the frail and elderly, children), many patients with medical conditions choose to fast during Ramadan. This may affect how they take their prescribed medications. Thus, healthcare professionals should be prepared to help these patients manage their medication regimens safely while fasting.

If patients decide to fast, they must be educated regarding the best time to take any oral medications that reach the stomach, particularly if drug absorption can be affected by food intake. As a general rule, medications that are dosed once or

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In a second case, a patient was prescribed semaglutide injection for weight loss. The patient received the compounded medication in a vial with instructions to inject 0.05 mL (5 units) using an insulin syringe. The patient did not understand the instructions and injected 0.5 mL (50 units). Later, they presented to an ED with severe abdominal pain, nausea, vomiting, and diarrhea. The patient was unable to verify the product's concentration. The reporter also noted that there had been an increase in ED visits by patients experiencing accidental overdoses after using insulin syringes to prepare their own doses of semaglutide from compounded vials.

A patient also reported to ISMP that they had been undergoing weight-management therapy with a provider at a weight-loss clinic. They reported receiving 12 clinic-prepared syringes containing tirzepatide and L-arginine in an unlabeled plastic bag. The patient noted that the volumes in the syringes (the syringes contained 1 to 1.5 mL) were different than the volume (2.5 mL) contained in syringes obtained from a previous provider. The patient was concerned about the risk of being underdosed, especially because they did not lose the anticipated amount of weight in a little more than a month. When the patient questioned the clinic staff about the compounded product and requested a refund for the next batch of syringes, the clinic staff became upset and called the police.

While the *Federal Food Drug and Cosmetic (FD&C) Act* prohibits pharmacies from compounding drug products that are essentially copies of a commercially available drug product, compounding pharmacies may prepare compounded versions of a drug if it appears on the FDA's drug shortage list and is thus not considered to be "commercially available." The compounders must also ensure that they meet certain conditions in the FD&C Act. Community pharmacies, licensed pharmacists, and licensed physicians are allowed to compound versions of an approved drug product that is not commercially available using bulk drug substances if the substances:[7]

- Comply with the standards of an applicable USP or National Formulary (NF) monograph, if a monograph exists; and the USP chapter on pharmacy compounding;
- If a monograph does not exist, components of drugs must be approved by FDA; or
- If a monograph does not exist and the bulk drug substances are not components of a drug approved by FDA, they must appear on a list developed by FDA through regulations (the 503A Bulks List).

Similarly, licensed compounding or outsourcing facilities are allowed to compound versions of an approved drug product that is not commercially available using bulk drug substances or active pharmaceutical ingredients (APIs) as long as the bulk substance meets the following criteria:[7]

- It appears on a list established by FDA identifying bulk drug substances for which there is a clinical need (the 503B Bulks List); or
- The drug compounded from such bulk drug substances appears on FDA's drug shortage list at the time of compounding, distribution, and dispensing.

FDA has informed the public and ISMP has seen reports in the media and on social media that some compounders are not using the same bulk drug substance that Novo Nordisk uses for its commercially available semaglutide products. Both Ozempic and Wegovy are produced using the base form of semaglutide. However, some compounders appear to be using a salt form of semaglutide, including semaglutide sodium and semaglutide acetate.[5] The use of the salt formulations of semaglutide may contribute to the compounded products having different strengths or concentrations than commercially available products. Also, compounded preparations produced using the semaglutide salts have not been shown to be safe and/or effective. Furthermore, semaglutide salts are not the subject of an applicable USP or NF monograph; are not components of an FDA-approved drug product currently on the FDA's drug shortage list; and do not appear on either the 503A Bulks List

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twice daily can be taken before or with the morning meal (suhoor) and/or with or after the evening meal (iftar). A physician will need to assess the risk versus benefit profile of medications that require three or more daily doses and determine the safest administration plan, including the possibility of switching to a slow-release or once daily medication. Patients should be advised to consult a pharmacist if they have questions.

Because teaching may differ regarding which routes of medication administration nullify the fast, specifically ask your patients what routes of administration are acceptable for use without breaking their fast. For example, some teaching may allow administration of eye and ear drops, nasal sprays, asthma inhalers, skin creams, transdermal patches, or subcutaneous injections while fasting, whereas others may not.

For patients with diabetes who choose to fast, dose modifications for insulin or other antidiabetic medications may be necessary. Blood glucose testing should occur throughout the day, and patients should be instructed to break the fast for a blood glucose level less than 70 mg/dL or greater than 300 mg/dL, for symptoms of hypoglycemia or hyperglycemia, or if acute illness occurs. Additional suggestions for managing medications for fasting patients with diabetes, cardiovascular disease, gastrointestinal health issues, or renal disease can be found at: www.ismp.org/ext/252. Also, examples of handouts for patients with diabetes can be found at: www.ismp.org/ext/253 (English) and www.ismp.org/ext/254 (Arabic).

Demonstration inhalers dispensed to patients. A pharmacy that keeps demonstration albuterol inhalers in stock to help teach patients how to use them reported that they had mistakenly dispensed the demonstration inhalers to multiple patients. The patients were contacted about the error and instructed to return the demonstration devices to the pharmacy or discard them. No administration errors were reported.

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or 503B Bulks List.[7] Therefore, compounded products using semaglutide salts are not exempt from certain sections of the FD&C Act, including the requirements of premarket approval and labeling with adequate directions for use, and therefore should not be marketed.[7,8]

Counterfeit Semaglutide Products

There have also been reports of counterfeit semaglutide products being distributed in the United States and globally. The FDA has reported they have seized thousands of units of suspected counterfeit Ozempic 1 mg packages.[9] FDA and Novo Nordisk are evaluating the seized products to determine the identity of the contents. Australian, Belgian, and Lebanese regulators have also reported counterfeit semaglutide products that were found to contain or were thought to have contained insulin.[10] Some patients who received these counterfeit products developed hypoglycemia and required hospitalization.

Wrong Strength Errors

When beginning therapy with approved GLP-1 receptor agonists, whether it is to treat type 2 diabetes or for chronic weight management, patients are started on a low dose and then titrated up to a maintenance dose over several months. For example, patients begin Wegovy treatment by injecting 0.25 mg subcutaneously once a week for 4 weeks. They then go through an escalation phase using 0.5 mg, 1 mg, and 1.7 mg for 4 weeks each before entering the maintenance phase of treatment at week 17 where they will inject 2.4 mg (or 1.7 mg) weekly.

ISMP has learned from practicing pharmacists that some prescribers order multiple strengths of a GLP-1 receptor agonists at one time anticipating a smooth titration of the drug. Sometimes these are sent as separate prescriptions and sometimes all are included in a single prescription. Unfortunately, there have been cases where the pharmacy has accidentally dispensed the wrong strength (e.g., an escalation strength instead of the starting strength) at the wrong time. This can increase the risks of adverse reactions such as nausea, diarrhea, vomiting, and abdominal pain.

Safe Practice Recommendations: Pharmacists and providers are in a position to help patients navigate the complexities of the current drug shortages of semaglutide, liraglutide, and tirzepatide. Consider the following recommendations when you are addressing the drug shortage situation with staff and patients, and if you are considering preparing compounded versions of these drugs.

Providers and Pharmacies

Provide one prescription for one strength at a time. While it may be convenient to issue prescriptions for multiple strengths at the same time, the safety of this practice is concerning. Ideally, only one prescription for the current dosage strength should be sent to a licensed pharmacy. This will help reduce the risk of the pharmacy dispensing the wrong strength for the patient's current stage of therapy or potentially dispensing all escalating strengths at the same time. Also, practitioners should provide clear directions to the patient when their prescribed dose changes and ensure those directions are understood. For example, with Rybelsus, prescribers should include instructions for the 7 mg tablets to begin after the 3 mg tablet prescription supply is exhausted (after 30 days). If prescriptions for both Rybelsus 3 mg and 7 mg must be provided at the same time, the statement, "Begin taking after [date]" should be included in the Rybelsus 7 mg directions. Pharmacists should make sure the patient has received these explicit instructions verbally and in writing. Use the teach-back method to verify that the patient understands, and can demonstrate, how to properly administer oral and injectable GLP-1 receptor agonists and manage dose changes.

Educate patients. Pharmacists should provide patient counseling when dispensing GLP-1 receptor agonists and verify with the patient their current stage of the dose escalation schedule. Also,

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The pharmacy noted that the packaging of the demonstration product is similar to the actual drug product. In fact, the demonstration cartons contained national drug code (NDC) numbers and barcodes that were able to be scanned in the pharmacy dispensing system. The only difference was that the demonstration product packaging did not include lot numbers or expiration dates. The reporter also noted that there was no notation on the carton or device that it was for demonstration purposes only.

To help prevent errors with demonstration products, manufacturers should not produce and distribute demonstration products without clearly identifying on the product label that it is for demonstration purposes only and contains no medication. They should also not include NDC numbers or barcodes that can be scanned by pharmacy dispensing systems. Pharmacies should evaluate whether demonstration devices are needed to support patient education. In most cases, using the actual product or other resources (e.g., videos) may be used to successfully teach patients how to use the medication and/or device. If demonstration products are used, develop processes to guide the procurement and storage of these products. Add an auxiliary label stating, "For Demonstration Only" or "For Simulation Only" to these products and store them away from actual medications or solutions.

Report safety issues with tobacco products to FDA. Nicotine is a highly addictive substance and can be found in products such as cigarettes, cigars, and e-cigarettes. Nicotine can cause serious health problems such as lung cancer. In 2009, the *Family Smoking Prevention and Tobacco Control Act* became law. This law gives the Center for Tobacco Products (CTP) within the US Food and Drug Administration (FDA) the authority to regulate the manufacturing, distribution, and marketing of tobacco products. Its goal is to stop the use of tobacco products and to keep consumers as safe as possible if they choose to use them.

The CTP takes a comprehensive approach to reduce the negative health effects of

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for those patients already using a GLP-1 receptor agonist and for those who express interest in exploring their use, it is important for both providers and pharmacists to teach patients about the risk that some externally compounded products may pose. If the patient is interested in using the products for weight loss (and not management of diabetes), discuss the possibility of delaying treatment until commercially available products are readily available to reduce the risk posed by some externally compounded products. Educate patients that GLP-1 receptor agonists, even when used for weight loss, should only be obtained with a valid prescription, and their therapy should be managed closely by the prescribing provider. Advise them about the potential adverse effects of the drugs and when to follow up with providers for intervention. Encourage patients to obtain prescription drugs only from state-licensed pharmacies that are located in the United States. Share FDA's BeSafeRx campaign (www.ismp.org/ext/618) with patients. This provides valuable information about how to safely buy prescription medicines online.

Educate staff. Provide education to providers, nurses, and pharmacy staff about the best clinical practices for managing GLP-1 receptor agonist therapy in patients who are obese and overweight.[2] Share information about the risk with compounded weight-loss products with staff. Update providers and pharmacy staff about the drug shortages identified on the FDA[3] or American Society for Health-System Pharmacists[4] drug shortage websites on a regular basis. Provide staff education and resources to help support patients looking for one of these medications by answering patient questions about the compounded products and providing strategies to identify valid or counterfeit products and manage therapy.

Report adverse events, counterfeit products, and errors. Healthcare practitioners, patients, and compounders should report adverse events and/or quality problems with these medications to the FDA's MedWatch Adverse Event Reporting program (www.ismp.org/ext/609). Practitioners and consumers are also encouraged to report suspected counterfeit products to FDA by calling an FDA Consumer Complaint Coordinator (www.ismp.org/ext/1332) or completing a report online (www.ismp.org/ext/1333). Also, please continue to report any errors to ISMP (www.ismp.org/report-error/merp).

Pharmacies Considering Compounding Versions of these Drugs

Utilize compounding technology. Implement technological safeguards (e.g., intravenous workflow management systems) to minimize opportunities for human error during the sterile compounding process. For additional information, review the ***ISMP Guidelines for Sterile Compounding and the Safe Use of Sterile Compounding Technology*** (www.ismp.org/node/31362).

Verify current shortages and the legality of compounding the drug. Periodically check the FDA shortage list since compounding weight-loss medications will be prohibited if the FDA approved drug that was on shortage becomes listed as "currently available." Review sections 503A and 503B of the FD&C Act and USP General Chapter <797> P*harmaceutical Compounding – Sterile Preparations* to ensure your pharmacy and sterile compounding procedures meet current regulatory requirements and recommendations.

Verify the bulk drug substance or API. If you are making compounded versions of drugs on the FDA drug shortage list, ensure that the API received is a pharmaceutical grade product, accompanied by a valid certificate of analysis, and is sourced from an establishment registered with the FDA. Also, ensure the product purchased is the intended formulation (e.g., using base rather than salt). Confirm that the API meets other state and federal requirements to be able to be used to compound a drug currently in shortage. Pharmacies should be aware that pharmaceutical manufacturers may initiate legal proceedings against prescribers and compounders who are producing illegal drug products.

References appear in the right column >

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Prevent mix-ups with Keytruda look-alike cartons

KEYTRUDA (pembrolizumab) is a programmed cell death receptor-1 (PD-1) blocking antibody indicated to treat various cancers. The medication is available as a 100 mg/4 mL (25 mg/mL) solution in single-dose vials packaged in cartons containing either one or two vials. Adult patients typically receive either 200 mg once every three weeks or 400 mg once every six weeks until disease progression or unacceptable toxicity. For some indications, Keytruda should be stopped after either 12 or 24 months of therapy. While Keytruda is administered as an intravenous (IV) infusion, specialty pharmacies may ship the drug to hospitals or infusion clinics where the drug will be administered. Some specialty pharmacies associated with infusion clinics may also be involved in the preparation of the infusion.

A specialty pharmacy reported to us that the one- and two-vial cartons look alike and have caused confusion when dispensing the product. The pharmacy is concerned that the packaging similarities could contribute to an error. At this pharmacy, they had typically dispensed two of the single-vial cartons of Keytruda 100 mg/4 mL injection for patients receiving doses of 200 mg every three weeks. Recently, the pharmacy received a prescription written for "200 mg IV every 3 weeks #1." The prescription was entered into the dispensing system for the two-vial carton and filled by the technician. The pharmacist checking the order was accustomed to verifying two cartons for each order and thought an error may have occurred when they only received one carton. The national drug code (NDC) on the two-vial carton (0006-3026-04) was different than that on the one-vial carton (0006-3026-02), but the concentration printed on the carton was the same and the cartons looked nearly identical (**Figure 1**). Statements about the contents of each carton are small, easy to miss, and appear in different locations on the carton label (bottom left corner of the single-vial carton and upper right corner of the two-vial carton).

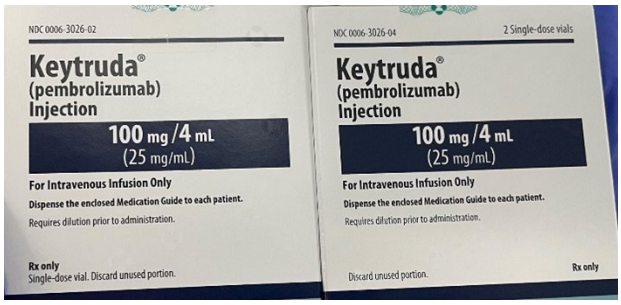

Figure 1. Keytruda 100 mg/4 mL cartons containing one (left) or two (right) vials look nearly identical and could be confused for one another. The number of vials inside each carton (bottom left corner of the carton on the left and upper right corner of the carton on the right) could easily be missed.

The pharmacy reported that their dispensing system, like many, does not require staff to scan the barcode on each medication container used to fill an order. For prescriptions that require two vials of Keytruda, they are concerned that staff could easily select one single-vial carton and one two-vial carton (300 mg instead of 200 mg), or select two two-vial cartons (400 mg instead of 200 mg) resulting in potential overdoses for patients. To reduce the risk of mix-ups, the pharmacy has separated the cartons in the refrigerator. They have also changed the description of the products in their dispensing system—100 mg/4 mL for one-vial carton and 200 mg/8 mL for the two-vial carton—to call attention to the differences. Pharmacies may also consider circling or highlighting the content statements on the cartons to draw attention to the differences.

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tobacco product use. They develop policy, issue regulations, conduct research, educate people on tobacco products, and make decisions on whether new tobacco products can be marketed—including the review and evaluation of applications to market products with reduced risk or exposure claims.

The CTP also monitors reports of health, quality, or safety issues associated with use or exposure to tobacco or nicotine products. Reports about unexpected tobacco-related health or product problems can help the FDA to identify and monitor known and emerging safety issues. Thus, they are asking the public to report any unexpected health problems (e.g., difficulty breathing, chest pain, poisonings) and other product-related issues, such as:

- Problems with e-cigarette batteries getting too hot, catching fire, or exploding
- Tobacco product mix-ups (such as labeling or packaging errors)
- Products that are broken, not working properly, stop working, or have an abnormal look, smell, or taste

Both practitioners and patients are encouraged to report any problems with tobacco products to FDA's CTP by using the online Safety Reporting Portal (www.ismp.org/ext/1292). To learn more about what to report and what to include in the report, visit: www.ismp.org/ext/1293. For the latest news and actions from the CTP, visit the CTP Newsroom (www.ismp.org/ext/1291).

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