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ISMP An ECRI Affiliate

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

Multiple error pathways with the monoclonal antibodies, casirivimab and imdevimab

Problem: On November 21, 2020, the monoclonal antibodies, casirivimab and imdevimab (**REGEN-COV**), received initial Emergency Use Authorization (EUA) from the US Food and Drug Administration (FDA). The two monoclonal antibodies are authorized to be administered together for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and children (12 years and older weighing at least 40 kg) with positive results of direct, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. The monoclonal antibodies are not authorized for use in patients who are hospitalized due to COVID-19, require oxygen therapy, or an increase in oxygen therapy if already receiving chronic oxygen therapy.

The EUA has been revised several times to address new safety information and to allow use for post-exposure prophylaxis of COVID-19 in adults and children (12 years and older and weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, and are not fully vaccinated or are not expected to mount an adequate immune response to vaccination. The EUA also allows post-exposure prophylaxis in individuals at high risk of exposure to another person infected with SARS-CoV-2 in the same institutional setting (e.g., nursing homes, prisons). Under the current EUA, the monoclonal antibodies can be administered either subcutaneously or intravenously (IV). The IV route is strongly preferred for treatment; however, either route is recommended for post-exposure prophylaxis. The subcutaneous route takes less time, facilitating administration, such as by pharmacists, and allowing for more widespread availability.

In a September 23, 2021 ***SAFETY* brief**, we mentioned possible confusion with a new alternative packaging for casirivimab and imdevimab (www.ismp.org/node/28427). Due to high demand for the monoclonal antibodies, Regeneron (manufacturer of REGEN-COV) is distributing co-packaged cartons of the antibodies that are manufactured by

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Submit self-assessment findings by December 10, 2021!

We want to thank the hospitals and ambulatory facilities that have already completed and submitted their assessment findings to ISMP for the ***ISMP Medication Safety Self Assessment® for Perioperative Settings***! If your facility has not yet submitted its information, there is still time. Once you submit your assessment findings to ISMP by **December 10, 2021**, you will receive your facility's weighted scores. If your facility submits its assessment findings by the deadline, you will also gain access to preliminary national data near the beginning of the first quarter of 2022 for comparing your scores to demographically similar facilities. Visit our perioperative assessment webpage (www.ismp.org/node/18027) to download a workbook of the full assessment with instructions for completion and data submission, and to access the online assessment required to submit your data to ISMP. Don't miss this unique opportunity to evaluate the safety of systems and practices within your organization and to document regulatory compliance. The aggregate assessment findings will be used to establish a baseline of national perioperative medication safety efforts and to inform the creation of ISMP national guidelines for medication safety in the perioperative setting.

SAFETY briefs

Age-related COVID-19 vaccine mix-ups. A November 4, 2021, ***SAFETY* brief** addressing the possibility of mix-ups between the pediatric formulation (orange cap and label border) and the formulation for individuals 12 years of age or older of the Pfizer-BioNTech coronavirus disease 2019 (COVID-19) vaccines (www.ismp.org/node/28303) has proven to be accurate, with multiple mix-ups reported to ISMP in just the past 2 weeks. Five reports described cases of underdosing in which 12-year-old children received doses appropriate for 5- to 11-year-old children (10 mcg/0.2 mL rather than 30 mcg/0.3 mL). In three of these cases, those administering the vaccine were unaware of the proper dose for 12-year-old children. Two cases were unexplained.

Conversely, there have been several reports of 5- to 11-year-old children who have received a higher dose intended for individuals 12 years and older. In one case, although a specific parental consent form was used for the 5- to 11-year-old age group, those administering the vaccine had not yet been made aware that a pediatric formulation existed, and that the dose was different for individuals 12 years and older. So, the children were given 30 mcg/0.3 mL of the Pfizer-BioNTech COVID-19 vaccine in error.

Another mix-up occurred due to a misunderstanding regarding the meaning of the letter P, intended to stand for "Pfizer" but mistaken as "pediatric," that was used on the syringe labels of **COMIRNATY**, the brand name for the US Food and Drug Administration (FDA)-approved Pfizer-BioNTech COVID-19 vaccine for ages 16 and older (doses for ages 12 to 15 years are approved under an Emergency Use Authorization [EUA]). The P was used to differentiate the Pfizer vaccine from the Moderna vaccine. The reasons for the remaining mix-ups were either not provided or attributed to high patient volumes.

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Regeneron's development partner, Roche Pharmaceuticals. The Roche co-packaged products are intended for distribution outside the US and use labeling that differs in some ways from Regeneron's other REGEN-COV products. In the ***SAFETY*** **brief**, we warned about possible confusion with the foreign Roche label because it lacks a National Drug Code (NDC) number, the product is labeled "For Pandemic Use" instead of "For EUA Use," and a barcode may not be present or functional. We also warned about confusion among the various presentations of the monoclonal antibodies.

Available Product Presentations

Currently, casirivimab and imdevimab are available in the US in a **co-formulated** vial containing both casirivimab and imdevimab together in the vial, **co-packaged** in cartons containing one vial of casirivimab and one vial of imdevimab, and in **Dose Pack bags** containing individual vials of casirivimab and imdevimab (**Table 1**).

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Table 1. Casirivimab and imdevimab packaging presentations

Presentation	Image	Contents
Co-formulated product in a single vial (REGEN-COV)		One single 10 mL vial contains 600 mg of casirivimab and 600 mg of imdevimab co-formulated (60 mg/60 mg per mL)
Co-packaged carton with one vial of casirivimab and one vial of imdevimab*		Two vials per carton: One vial of casirivimab One vial of imdevimab Co-packaged cartons include either 2.5 mL vials (300 mg each) **or** 11.1 mL vials (1,332 mg each) Concentration of the product in each vial is 120 mg/mL
Dose Pack bag with individual vials of casirivimab and imdevimab (REGEN-COV)		Contains two, five, or eight cartons, providing at least a total of 2,400 mg of casirivimab and imdevimab (1,200 mg of casirivimab and 1,200 mg of imdevimab) and a one-page informational document† Concentration of the product in each vial is 120 mg/mL

* *The co-packaged cartons are manufactured by Regeneron's development partner Roche Pharmaceuticals and are being distributed by Regeneron to increase the availability of doses of casirivimab and imdevimab.*

† *The included one-page informational document contains inaccurate dosing information per the current Health Care Provider Fact Sheet. The QR code on the document can be used to obtain the most current Fact Sheet.*

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There were also some children ages 5 to 11 years for which the 30 mcg/0.3 mL Pfizer-BioNTech vaccine (intended for individuals 12 years and older) was used but was thought to be acceptable if only 10 mcg was given, either as 0.1 mL of the 30 mcg/0.3 mL vaccine (10 mcg), or by diluting the 10 mcg dose in a syringe to 0.2 mL. In one event reported via the news media, 112 children ages 5 to 11 years received their vaccine in this manner. Neither method would be correct, though, since the pediatric vaccine is specifically formulated to be more diluted to ensure accurate measurement. Withdrawing 0.1 mL in a 1 mL syringe will result in an inaccurate volume, as it is recommended that no less than 20% of the nominal syringe capacity is measured to limit instrumental error. Also, if a needle different from the one used for drawing up the vaccine is used for administration, some of the 0.1 mL dose would likely be lost to dead space in the needle. If a 0.1 mL dose is drawn up and the same needle and syringe are used to draw up a 0.9% sodium chloride diluent, then the vaccine initially in any dead space of the needle and syringe hub would be drawn into the syringe as it is pulled back to withdraw the diluent. Depending on how evenly the vaccine is distributed in the syringe, this could result in too much or too little vaccine reaching the patient upon injection.

ISMP also received a report in which a hospital requested numerous physician offices to schedule 5- to 11-year-old children for the Pfizer-BioNTech 30 mcg/0.3 mL vaccine because the vials were expiring soon, with the misunderstanding that 10 mcg doses could be prepared from that formulation for the younger children. However, ISMP was unable to confirm if any doses were actually administered in this manner. Additionally, ISMP is following up on two error reports received this week, one involving 14 children (ages 5 to 11), who received vaccine meant for individuals 12 years and older, and the other involving 22 children (ages 5 to 11) who also received vaccine meant for the older age group.

For additional information and recommended error-prevention strategies, please see our November 4, 2021, ***SAFETY*** **brief** available here: www.ismp.org/node/28303.

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Risk of Errors

We are hearing that many nurses have been tasked with selecting these monoclonal antibodies from automated dispensing cabinets (ADCs) and then preparing and administering them. Furthermore, the locations where casirivimab and imdevimab are administered (e.g., infusion centers, clinics, emergency departments, long-term care facilities, prisons) are extremely busy, and the staff are often rushed, increasing the risk of an error. Under these conditions, we have received numerous reports of confusion as well as actual errors. Most of the errors are associated with preparing and administering only one component of the two monoclonal antibodies, or prescribing, preparing, and/or administering the wrong dose. Common causes of this confusion and examples of the error reports we have received just in the past few weeks are summarized below.

Common Causes of Confusion and Errors

Prescribing errors. The monoclonal antibodies have been prescribed using an ambiguous dose designation of "600 mg" instead of the recommended "600 mg of casirivimab and 600 mg of imdevimab" (or "300 mg of casirivimab and 300 mg of imdevimab" for certain post-exposure prophylaxis circumstances). A common contributing factor associated with these prescribing errors is misleading order entry fields that do not make it clear that 600 mg (or 300 mg) of EACH monoclonal antibody is required for appropriate dosing. Based on error reports we have received, a knowledge deficit about the recommended dose has infrequently been an underlying cause of prescribing errors.

Selection errors. Organizations may not have a choice of which product presentation they receive. Thus, given the various presentations of the monoclonal antibodies and the fact that they are often stored together, selection errors among the different presentations have been occurring in both the pharmacy and in patient care areas where the antibodies might be prepared. For example, mix-ups between vials of the co-formulated antibodies and vials of the individual antibodies have been reported.

Preparation errors. Some preparation errors have been related to label confusion. Displayed on the front panel of the Roche label for the co-packaged cartons containing 2.5 mL or 11.1 mL vials of casirivimab and imdevimab is "2 vials of 6 mL" or "2 vials of 20 mL," respectively (see the red arrows on the images in **Table 1**, page 2), which refers to the vial size, not the contents of each vial or the sum of the two vial contents. Confusion about the volume in each vial could lead to preparation of incorrect doses. ISMP has received several reports regarding this particular label confusion. One reported error involved a pharmacy technician who withdrew the contents of both casirivimab and imdevimab from the Roche co-packaged 2.5 mL vials. Upon discovering that the total volume was only 5 mL instead of 6 mL (which was listed on the front label panel), the technician thought she did not have enough medication to prepare a 600 mg total dose (300 mg of each monoclonal antibody) for repeat dosing intended for post-exposure prophylaxis.

Confusion has also been reported regarding the total contents of the 10 mL vial of the co-formulated monoclonal antibodies. Some have mistakenly thought that the co-formulated product contains 300 mg of each antibody (600 mg total), when it actually contains 600 mg of each antibody (1,200 mg total). In one reported error, a nurse retrieved the co-formulated product and misunderstood "600 mg/600 mg per 10 mL" on the label to mean that each 10 mL vial contained 600 mg in total (300 mg of casirivimab and 300 mg of imdevimab). She then retrieved a second vial of the co-formulated product and mixed the two 10 mL vials in a 100 mL infusion bag of 0.9% sodium chloride injection, thus administering an overdose. Confusion

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HIGH-ALERT

Safe use of parenteral nutrition. The American Society for Parenteral and Enteral Nutrition (ASPEN) has published recommendations on the safe use of lipid injectable emulsions (ILEs). Part 1 of this two-part series (www.ismp.org/ext/807) provides a comprehensive review of ILEs and considerations for use in adult patients, while part 2 (www.ismp.org/ext/808) focuses on neonatal- and pediatric-specific information. ASPEN also has published a position paper covering recommendations for photoprotection of parenteral nutrition (PN) for premature infants (www.ismp.org/ext/809). The paper reviews the scientific literature on the formation of quantifiable peroxides and other degradation products when PN admixtures and ILEs are exposed to light and reports of adverse clinical outcomes in premature infants subjected to light-exposed PN. Recommendations for photoprotection of PN admixtures and ILEs are provided, as well as the challenges in achieving complete photoprotection with the equipment, supplies, and materials currently available in the US. In addition, there is an invited commentary (www.ismp.org/ext/810) on the international perspective on photoprotection.

Labeling of transdermal scopolamine products. A pharmacist was replacing transdermal scopolamine in an automated dispensing cabinet (ADC) and noticed that the replacement product (from Perrigo) expressed the amount of drug in terms of how much was released over 3 days (1 mg/3 days). In the past, the transdermal scopolamine they had purchased (from Sandoz) had been labeled in terms of the amount of scopolamine contained in the patch (1.5 mg) (**Figure 1**). Also, the hospital's electronic order entry system listed transdermal scopolamine as 1.5 mg and displayed this amount on the medication administration record (MAR) and

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Figure 1. TRANSDERM SCŌP (scopolamine) on the left (Sandoz) lists the strength as total drug content (1.5 mg), while a generic product on the right (Perrigo) expresses the strength by release rate (1 mg/3 days), as per an FDA draft guidance.

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has also been reported regarding whether each vial contains the co-formulated monoclonal antibodies (both antibodies) or contains a single antibody.

Errors related to the various instructions for preparation following Regeneron's *Fact Sheet* (www.ismp.org/ext/779) have also been reported. For the recommended IV infusion route of administration, a 10 mL (600 mg/600 mg) vial of the co-formulated product, or 5 mL of casirivimab (600 mg) and 5 mL of imdevimab (600 mg) from individual antibody vials, must be injected into a 50 mL, 100 mL, 150 mL, or 250 mL, single 0.9% sodium chloride or 5% dextrose infusion bag, each with a different minimum infusion time and the 50 mL bag with a different rate of infusion. We have heard about nurses who have prepared each monoclonal antibody in a separate infusion bag, rather than preparing them together in a single bag. We also learned about a nurse who selected two 2.5 mL vials of imdevimab (each labeled 300 mg/2.5 mL) and prepared and administered them without the casirivimab component, misunderstanding the "600 mg" dose designation that was listed on the patient's medication administration record.

The various presentations of these monoclonal antibodies, and the fact that some co-packaged dose packs contain enough product for two full doses instead of just one full dose, increases the risk of an error. Also, we are not confident that vials of the monoclonal antibodies that are stored under refrigeration are consistently being brought to room temperature as directed for 20 minutes prior to dilution or subcutaneous injection.

For administration by the subcutaneous route, different preparation directions are provided in the *Fact Sheet*. If using a casirivimab and imdevimab co-formulated 10 mL vial, four separate syringes (2.5 mL each) must be prepared for 600 mg of casirivimab and 600 mg of imdevimab (or two syringes for 300 mg doses of each antibody). If using casirivimab and imdevimab individual vials, two separate syringes (2.5 mL each) must be prepared for both casirivimab and imdevimab (for a total of four syringes) to provide a 600 mg dose of each antibody (or just one syringe of each for a total of two syringes for 300 mg doses of each antibody). While we have not received any reported errors regarding preparation of the monoclonal antibodies for the subcutaneous route of administration, we worry that errors might be occurring, and the syringes might not be labeled during preparation in patient care areas.

Administration errors. Most of the reported administration errors we received have been noted above (e.g., wrong doses, administering just one monoclonal antibody instead of both, wrong rates of infusion [dependent on bag size]). We have also received reports where the four syringes prepared for subcutaneous administration were administered at the same injection site instead of different injection sites as recommended. It is also unclear how the most up-to-date information in the current casirivimab and imdevimab *Fact Sheet* is being conveyed to frontline practitioners who have to prepare and administer the monoclonal antibodies, particularly since the *Fact Sheet* has been revised multiple times.

Safe Practice Recommendations: To reduce the risk of errors when prescribing, preparing, dispensing, or administering casirivimab and imdevimab, take the following precautions:

Clarify dosing during order entry. In order entry systems and on standardized order sets, make it clear that 600 mg (or 300 mg under certain conditions) of each antibody is required for appropriate dosing. Consider requiring the entry of an indication (e.g., treatment, post-exposure prophylaxis, repeat dose of post-exposure prophylaxis) and default to the appropriate dose based on the indication.

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the ADC screen, which is inconsistent with the current package labeling from Perrigo. The pharmacist thought that perhaps this was a new strength of scopolamine, but he noticed that online drug references such as *Lexicomp* and *Micromedex* indicate that a 1.5 mg patch delivers 1 mg of scopolamine over 3 days.

This situation has the potential to confuse pharmacists and nurses. However, a US Food and Drug Administration (FDA) draft guidance (www.ismp.org/ext/774, lines 340-341) calls for the strength of transdermal products to be expressed as a rate (e.g., 1 mg/ 3 days), instead of total drug content (e.g., 1.5 mg). FDA has been working to change all transdermal scopolamine product labeling to 1 mg/3 days rather than 1.5 mg. Until the labeling of all transdermal scopolamine products displays the new strength expression and older stock has been exhausted, the potential for confusion exists. Consider editing order entry systems, order sets, and MARs to indicate the drug delivery rate of 1 mg over 3 days, and during the availability of mixed labeling of these products, include a default note on the order that states, "1.5 mg = 1 mg/3 days."

Dosing error. A dosing error was reported with the prodrug isavuconazonium sulfate (**CRESEMBA**) capsules that led to a 50% lower dose than intended. Isavuconazonium is used to treat invasive aspergillosis and invasive mucormycosis in adults. The error happened when an infectious disease physician recommended starting a patient on "isavuconazole 200 mg PO every 8 hours for 6 doses as a loading dose, then continue at 200 mg PO daily." Isavuconazole is the active moiety. The hematology/oncology team member could only find isavuconazonium sulfate listed during order entry, so she started the patient on isavuconazonium sulfate 186 mg to get as close to 200 mg as possible. However, each isavuconazonium sulfate 186 mg capsule is only equivalent to isavuconazole 100 mg, so the patient received only half the intended dose. The proper dose required two capsules to be ordered for each dose (372 mg, or 200 mg of isavuconazole). A pharmacist missed the prescribing error and verified the incorrect dose. The patient received six incorrect doses before the error was recognized.

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Require pharmacy preparation. Whenever possible, outside of emergencies, have the pharmacy prepare and label patient-specific subcutaneous doses and IV infusions of the monoclonal antibodies, and dispense them to the appropriate patient care areas. If practitioners must prepare the doses in patient care areas, provide them with clear preparation instructions and preprinted labels for the subcutaneous syringes and the IV infusions.

Update EHRs with current information from the *Fact Sheet*. While it is not easy, for all EUA drugs, including casirivimab and imdevimab, it is important to assign an individual to regularly check the *Fact Sheets* for the most current information and to keep all electronic health record (EHR) systems updated with new information so it is readily available to all frontline practitioners. If questions arise, it is equally important for all practitioners prescribing, preparing, dispensing, and administering casirivimab and imdevimab to refer to the current *Fact Sheet* in case it has been revised. Revision dates and recent major changes are described within the first few pages of the *Fact Sheet*. Do not use the dosing and administration information on the one-page document in the Dose Packs because this information is not current.

Create separate storage. Separate the different presentations of the monoclonal antibodies in sequestered storage containers in the refrigerator and other storage locations, and clearly label each storage container. Consider packaging each complete dose in a separate, labeled ziplock bag.

Use auxiliary warnings. Include bold, colorful critical warnings on the product storage containers and on electronic screens or menus where these products are listed, based on the type of errors that have been reported. At a minimum, consider using these auxiliary warnings: "**Co-formulated casirivimab and imdevimab**," "**Co-packaged casirivimab and imdevimab** (must be **administered together**)," and "**Dose Pack** of **casirivimab and imdevimab** (must be **administered together**)."

Reduce confusion with the Roche co-packaged product. If you receive the Roche co-packaged monoclonal antibodies, educate staff about the label differences. Also, before product use, either place (if absent) or replace the barcode on the product with a pharmacy-prepared barcode, or test any available barcodes on the product and manually input the product information, including the NDC number, into your EHR system to ensure the barcodes do not provide incorrect information when the product is scanned. If questions arise, ensure staff know to reference the *Fact Sheet* intended for US administration rather than the package leaflet in the carton (which is not approved for use in the US and should be discarded). Also consider clarifying the volume of product contained in each vial using auxiliary labels.

Educate staff. Educate practitioners who prepare and administer the monoclonal antibodies, with a particular focus on the various presentations available, reported label confusion, the types of errors reported nationwide, and preparation and/or administration instructions from the most current *Fact Sheet*.

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The hospital is now adding a note in the computer that states, "isavuconazonium sulfate 186 mg = isavuconazole 100 mg," and is adding product comments to notify the pharmacist during verification to assist with dose checking. Cresemba is also available as an injection in vials of lyophilized powder for reconstitution containing 372 mg of isavuconazonium sulfate (equivalent to 200 mg of isavuconazole), which requires further dilution (250 mL of 5% dextrose or 0.9% sodium chloride) for infusion. The labeling for the capsules and vials indicates the mg amounts of both the salt (prodrug) and active moiety.

Special Announcement

FREE ISMP webinars

ISMP is presenting two **FREE** webinars on high-alert medications! The first, ***High-Alert Medications—Insulin and Vasopressors: Practical Strategies in Pursuit of Safety***, will be presented on **December 16, 2021**, and the second, ***High-Alert Medications—Heparin, Concentrated Electrolytes, and Magnesium: Practical Strategies in Pursuit of Safety***, will be presented on **January 25, 2022**. During both webinars, faculty will review the safety characteristics of these specific high-alert medications and identify opportunities for improvement based on findings from the ***ISMP Medication Safety Self Assessment® for High-Alert Medications***. Effective risk-reduction strategies will also be discussed. Continuing education (CE) credit has been approved and/or is being sought for both webinars. For details and to register for the December 2021 webinar, visit: www.ismp.org/node/28249. For details and to register for the January 2022 webinar, visit: www.ismp.org/node/28440.

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