View as a Web page

REGENERON

We are distributing this communication on behalf of Regeneron Pharmaceuticals, Inc.

On September 9th, 2021, the U.S. Food and Drug Administration (FDA) updated Regeneron's Emergency Use Authorization (EUA) to authorize an additional presentation of REGEN-COV™ (casirivimab and imdevimab) – specifically a co-packaged presentation of REGEN-COV that consists of individual vials of both casirivimab and imdevimab inside a single carton.

This alternative packaging contains individual antibody solutions of casirivimab and imdevimab in separate vials which are co-packaged in a carton labeled as "casirivimab and imdevimab 120 mg/mL concentrate for solution for infusion" and manufactured by Roche. Please be aware that the labels and labeling may cause some users to mistakenly believe that the vials contained within the carton are the co-formulated product and may contribute to confusion.

This co-packaged product will be distributed in addition to the current presentations of co-formulated REGEN-COV and dose packs of individual vial cartons of casirivimab and imdevimab. The co-packaged cartons were manufactured by Regeneron's development partner Roche Pharmaceuticals for distribution outside the United States; however, some will be distributed by Regeneron, to increase the available doses of casirivimab and imdevimab as we continue to combat the ongoing COVID-19 public health emergency. These casirivimab and imdevimab co-packaged cartons produced by Roche are available for pandemic use in the European Union. **The cartons include the same monoclonal antibodies that are authorized for use in the U.S. under REGEN-COV's Emergency Use Authorization (EUA)** and distributed as REGEN-COV co-formulated product or dose packaging of individual vial cartons. All other presentations of REGEN-COV may still be in inventory or distribution.

Images of the new co-packaged presentations of REGEN-COV are included below. Further instructions on the preparation of REGEN-COV are available on regencov.com, and in the **Fact Sheet for Healthcare Providers**.

AUTHORIZED USE

TREATMENT
The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Limitations of Authorized Use

- REGEN-COV is not authorized for use in patients:
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR
  - who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity
- Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high-flow oxygen or mechanical ventilation

POST-EXPOSURE PROPHYLAXIS
The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[1] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[2]) **and**
- have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[3] **or**
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons)

Limitations of Authorized Use

- Post-exposure prophylaxis with REGEN-COV (casirivimab and imdevimab) is not a substitute for vaccination against COVID-19.
- REGEN-COV (casirivimab and imdevimab) is not authorized for pre-exposure prophylaxis for prevention of COVID-19.

REGEN-COV has been authorized by FDA for the emergency uses described above.

REGEN-COV is not FDA approved for these uses.

REGEN-COV is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of REGEN-COV under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb 3(b)(1), unless the authorization is terminated or revoked sooner.

Healthcare providers should review the **Fact Sheet for Healthcare Providers** for information on the authorized uses of REGEN-COV and mandatory requirements of the EUA and must comply with the requirements of the EUA. The **FDA Letter of Authorization** is available for reference, as well as the **Dear Healthcare Provider Letter** and **Patient Fact Sheet**

Criteria for Identifying High Risk Individuals
Please refer to the Fact Sheet for Healthcare Providers for criteria for identifying high risk individuals

SARS-CoV-2 Viral Variants
Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. Healthcare providers should review the Antiviral Resistance information in Section 15 of the Fact Sheet for details regarding specific variants and resistance, and refer to the CDC website as well as information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

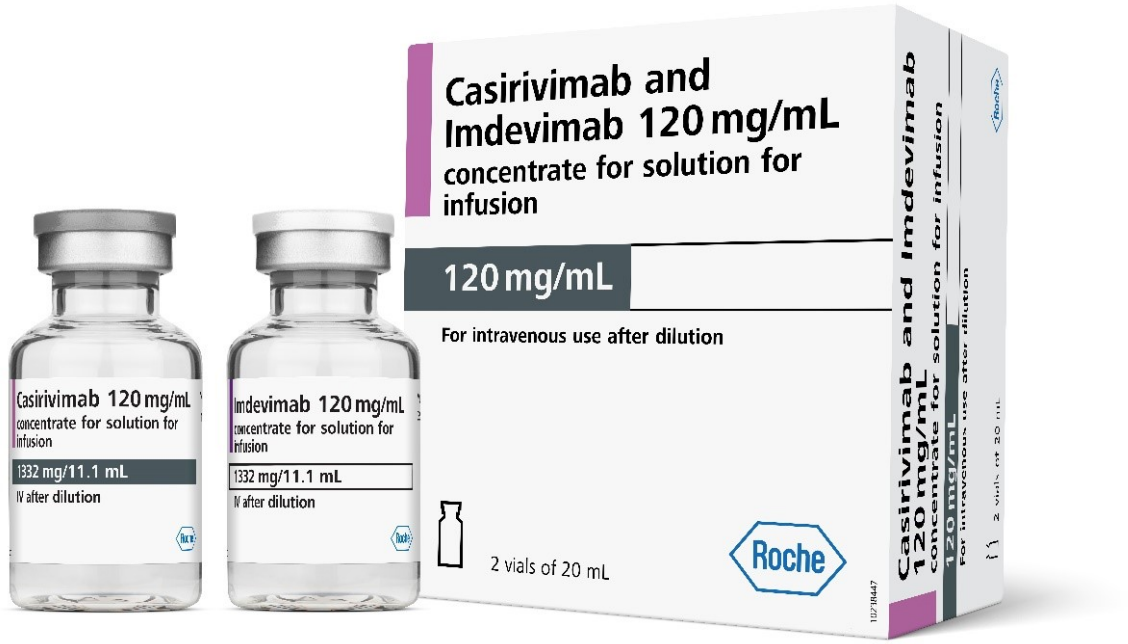
Each Roche co-packaged carton contains individual antibody solutions in separate vials as follows (shown in Figure 1 and Figure 2 below):

- **One (1)** vial containing casirivimab; 300 mg/2.5 mL (120mg/mL) or 1,332 mg/11.1 mL (120 mg/mL)
- **One (1)** vial containing imdevimab; 300 mg/2.5 mL (120mg/mL) or 1,332 mg/11.1 mL (120 mg/mL)

Figure 1. Roche-manufactured Co-packaged Casirivimab (300 mg/2.5mL) and Imdevimab (300 mg/2.5mL)

Although the carton is labeled "2 vials of 6 mL," this is referring to the vial size and not the content of the vial. This presentation contains 2 vials of 2.5 mL (one of casirivimab and one of imdevimab).

Figure 2. Roche-manufactured Co-packaged Casirivimab (1332mg/11.1mL) and Imdevimab (1332mg/11.1mL)



Although the carton is labeled "2 vials of 20 mL," this is referring to the vial size and not the content of the vial. This presentation contains 2 vials of 11.1 mL (one of casirivimab and one of imdevimab).

Healthcare providers should be aware that the casirivimab and imdevimab formulations in individual vials in the co-packaged carton can be prepared and administered **the same** as the formulations in the individual vials in the REGEN-COV dose pack.

The Healthcare Provider (HCP) Fact Sheet is enclosed with this letter for reference to the full prescribing information. Stay current with the latest Fact Sheet for Health Care Providers by visiting (https://www.regeneron.com/sites/default/files/treatment-covid19-eua-fact-sheet-for-hcp.pdf).

All formulations and presentations of casirivimab and imdevimab or REGEN-COV can be used to prepare treatment or post-exposure prophylaxis doses for intravenous infusion or subcutaneous injection. Under the EUA, more than one dose may be prepared from the vials, according to the specific instructions in the FDA-authorized EUA HCP Fact Sheet. Refer to the EUA HCP Fact Sheet for product preparation, administration, and storage information.

Key Differences Between Roche's Co-Packaged Vials of Casirivimab and Imdevimab and Other Presentations of REGEN-COV.

- The carton for Roche's co-packaged product is labeled as "casirivimab and imdevimab 120 mg/mL concentrate for solution for infusion". **Do not confuse this co-packaged carton with REGEN-COV (casirivimab and imdevimab) co-formulated solution.**
- The vials in the co-packaged carton may be used to prepare and administer intravenous infusions as well as subcutaneous injections despite having the statements such as "Concentrate for solution for infusion" or "For intravenous infusion after dilution".
- Inside the co-packaged carton there is a folded package leaflet which is not approved for US use. **Discard** the "package leaflet" included inside the carton and **refer to the EUA HCP Fact Sheet for current information.**
- Inside the shipment there is a one-page "Co-Packaged Product Quick Reference Guide" that provides a QR code that leads to the current U.S. HCP Fact Sheet and other key information related to the co-packaged presentation. A copy of the one-page document is appended to this letter.
- The carton and vial labels of co-packaged casirivimab and imdevimab do not include an NDC number. An NDC number is provided on the one page "Co-Packaged Product Quick Reference Guide" that is shipped with the product.
- **The barcode on the co-packaged carton labeling may not register with U.S. scanning systems and may not be functional for identifying the drug products.** There is no barcode on the co-packaged vial labels. Institutions should manually input the product information into their systems to confirm the barcode systems do not provide incorrect information when the product is scanned.
- Each co-packaged carton will be labeled with the names of the individual monoclonal antibodies only (i.e., casirivimab or imdevimab) and will not include the brand name "REGEN-COV".
- Roche is listed as the manufacturer instead of Regeneron.
- The cartons say "For pandemic use" instead of for EUA use.

INVENTORY MANAGEMENT OF CO-PACKAGED CARTONS OF CASIRIVIMAB AND IMDEVIMAB

Barcodes
Linear barcodes on the co-packaged cartons may not register with U.S. scanning systems and may not be functional for identifying the drug products. Co-packaged vials do not have a barcode.

NDCs
NDCs are not printed on vials or carton for the Roche co-packaged presentation. An NDC number is provided on the one page "Co-Packaged Product Quick Reference Guide" that is shipped with the co-packaged product (also see Table 1 below). Be aware that the NDCs assigned for co-packaged carton are unique and should be added to appropriate systems for inventory management. Vial NDCs in the co-packaged cartons that are provided on the one page "Co-Packaged Product Quick Reference Guide" are the same NDCs for the individual vials of casirivimab and imdevimab included in the REGEN-COV dose packs.

Update your systems accordingly to reflect these NDCs.

Table 1: NDCs for Co-Packaged Product

Co-Packaged Carton Contents	Co-Packaged Components	Concentration	Co-Packaged Carton NDC Number
2 Vials*	**1 vial of casirivimab** (NDC 61755-024-00)	1,332 mg/11.1 mL (120 mg/mL)	61755-042-02
	1 vial of imdevimab (NDC 61755-025-00)	1,332 mg/11.1 mL (120 mg/mL)	
2 Vials	**1 vial of casirivimab** (NDC 61755-026-00)	300 mg/2.5 mL (120 mg/mL)	61755-045-02
	1 vial of imdevimab (NDC 61755-027-00)	300 mg/2.5 mL (120 mg/mL)	

* More than one dose may be prepared from the vials, according to the instructions in the FDA-authorized EUA HCP Fact Sheet.

HEALTHCARE PROVIDER ACTION

- Stay current with the latest Fact Sheets for Health Care Providers (https://www.regeneron.com/sites/default/files/treatment-covid19-eua-fact-sheet-for-hcp.pdf)
- In light of the additional presentation, healthcare providers should update their Electronic Health Records (EHRs) with the new product information to allow for the use of available co-packaged cartons to prepare doses for intravenous infusion or subcutaneous injection for treatment or post-exposure prophylaxis.
- Create alerts, directed at healthcare providers, in the electronic health record (EHR) systems that if preparing an intravenous infusion with individual vials of casirivimab and imdevimab, they must be administered together after dilution.
- Create alerts, directed at healthcare providers, in the electronic health record (EHR) systems that if preparing subcutaneous injections that the individual syringes should be labeled to ensure the patient receives all syringes needed of each antibody for a single dose.
- Store REGEN-COV (casirivimab with imdevimab) co-packaged cartons in the refrigerator in the original carton and away from other COVID-19 vaccines and drug products. **Do not open co-packaged cartons until the time at which the intravenous infusion or the subcutaneous injections will be prepared.**
- Do not comingle co-formulated REGEN-COV cartons with co-packaged REGEN-COV cartons.
- **Due to multiple presentations of REGEN-COV (co-formulation in a single vial, dose-pack bags, and co-package cartons) it is important to educate staff on the different presentations and how to prepare doses appropriately with each presentation.**
- **The barcode on the co-packaged carton label may not register with U.S. scanning systems.** There is no barcode on the co-packaged vial labels. Institutions should manually input the product information into their systems to confirm the barcode systems do not provide incorrect information when the product is scanned. Alternative procedures, including checking the label information manually and/or applying site-generated barcodes, should be instituted to assure that the correct drug product is being used for dose preparation.

Resources to help clarify dose preparation can be found on www.REGENCOV.com.

Reporting Adverse Events and Medication Errors

Under the EUA, all serious adverse events and all medication errors potentially related to casirivimab and imdevimab must be reported within 7 calendar days from the onset of the event. Serious adverse event reports and medication error reports should be submitted to FDA's MedWatch program using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
- Complete and submit a postage-paid Form FDA 3500 (https://www.fda.gov/media/76299/download) and return by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 208529787, or by fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form.

Please provide a copy of all FDA MedWatch forms to Regeneron via fax (1-888-876-2736) or email (medical.information@regeneron.com).

Healthcare providers should direct questions about REGEN-COV (casirivimab with imdevimab) packaging or use to the Regeneron Medical Information Department at 1-844-734-6643 or to medical.information@regeneron.com.

The EUA Fact Sheet for Healthcare Providers is included with this notice, available at www.REGENCOV.com, or available by scanning the QR Code below:

Important Safety Information

REGEN-COV (casirivimab and imdevimab) is an unapproved investigational therapy, and there are limited clinical data available. Serious and unexpected adverse events may occur that have not been previously reported with REGEN-COV use

- **Contraindication**:
  REGEN-COV is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to REGEN-COV

- **Warnings and Precautions**:
  - **Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions:** Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of REGEN-COV. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy. Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of REGEN-COV under EUA. Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of REGEN-COV. These reactions may be severe or life threatening
    - **Signs and symptoms of infusion-related reactions may include:** fever, difficulty breathing, reduced oxygen saturation, chills, nausea, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness, fatigue and diaphoresis. Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion-related reaction occurs
  - **Clinical Worsening After REGEN-COV Administration:** Clinical worsening of COVID-19 after administration of REGEN-COV has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to REGEN-COV use or were due to progression of COVID-19
  - **Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19:** Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high-flow oxygen or mechanical ventilation. Therefore, REGEN-COV is not authorized for use in patients who are hospitalized due to COVID-19, OR who require oxygen therapy due to COVID-19, OR who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19–related comorbidity

- **Adverse Reactions**:
  - **COV-2067 (Treatment):** Infusion-related reactions (adverse event assessed as causally related by the investigator) of grade 2 or higher severity have been observed in 10/4,206 (0.2%) of those who received REGEN-COV at the authorized dose or a higher dose. Three subjects receiving the 8,000 mg dose of REGEN-COV, and one subject receiving the 1,200 mg casirivimab and 1,200 mg imdevimab, had infusion-related reactions (urticaria, pruritus, flushing, pyrexia, shortness of breath, chest tightness, nausea, vomiting, rash) which resulted in permanent discontinuation of the infusion. All events resolved. Anaphylactic reactions have been reported in the clinical program in subjects receiving REGEN-COV. The events began within 1 hour of completion of the infusion, and in at least one case required treatment including epinephrine. The events resolved
  - **COV-2069 (Post-exposure prophylaxis):** In subjects who were SARS-CoV-2 negative at baseline (Cohort A), injection site reactions (all grade 1 and 2) occurred in 55 subjects (4%) in the REGEN-COV group and 19 subjects (2%) in the placebo group. The most common signs and symptoms of injection site reactions which occurred in at least 1% of subjects in the REGEN-COV group were erythema and pruritus. Hypersensitivity reactions occurred in 2 subjects (0.2%) in the REGEN-COV group and all hypersensitivity reactions were grade 1 in severity. In subjects who were SARS-CoV-2 positive at baseline (Cohort B), injection site reactions, all of which were grade 1 or 2, occurred in 6 subjects (4%) in the REGEN-COV group and 1 subject (1%) in the placebo group. The most common signs and symptoms of injection site reactions which occurred in at least 1% of subjects in the REGEN-COV group were ecchymosis and erythema
  - **COV-2093 (Subcutaneous Dosing):** Injection site reactions occurred in 12% and 4% of subjects following single dose administration in the REGEN-COV and placebo groups, respectively. Remaining safety finding following subcutaneous administration in the REGEN-COV group were similar to the safety findings observed with intravenous administration in COV-2067. With repeat dosing, injection site reactions occurred in 252 subjects (35%) in the REGEN-COV group and 38 subjects (16%) in the placebo group; all injection site reactions were grade 1 or 2 in severity. Hypersensitivity reactions occurred in 8 subjects (1%) in the REGEN-COV group; and all hypersensitivity reactions were grade 1 or 2 in severity. There were no cases of anaphylaxis

- **Patient Monitoring Recommendations**: Clinically monitor patients during dose administration and observe patients for at least 1 hour after intravenous infusion or subcutaneous dosing is complete

- **Use in Specific Populations**:
  - **Pregnancy:** There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. REGEN-COV should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus
  - **Lactation:** There are no available data on the presence of casirivimab and/or imdevimab in human milk or animal

milk, the effects on the breastfed infant, or the effects of the drug on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for REGEN-COV and any potential adverse effects on the breastfed child from REGEN-COV or from the underlying maternal condition

Dosage

Treatment:
The authorized dosage is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion or by subcutaneous injection as soon as possible after positive SARS-CoV-2 viral testing and within 10 days of symptom onset.

Post-Exposure Prophylaxis:
The authorized dosage is 600 mg of casirivimab and 600 mg of imdevimab administered by subcutaneous injection or together as a single intravenous infusion as soon as possible following exposure to SARS-CoV-2.

For individuals in whom repeat dosing is determined to be appropriate for ongoing exposure to SARS-CoV-2 for longer than 4 weeks and who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination, the initial dose is 600 mg of casirivimab and 600 mg of imdevimab by subcutaneous injection or intravenous infusion followed by subsequent repeat dosing of 300 mg of casirivimab and 300 mg of imdevimab by subcutaneous injection or intravenous infusion once every 4 weeks for the duration of ongoing exposure.

For Intravenous Infusion:

- Co-formulated casirivimab and imdevimab solution in a vial and casirivimab and imdevimab solutions in individual vials must be diluted prior to intravenous administration.
- Administer casirivimab and imdevimab together as a single intravenous infusion via pump or gravity (see Fact Sheet for Healthcare Providers Table 1, Table 2, Table 3 and Table 4).
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

For Subcutaneous Injection:

- Administer casirivimab and imdevimab using the co-formulated solution in a vial or using the individual vials (see Fact Sheet for Healthcare Providers Table 5, Table 6).
- Clinically monitor patients after injections and observe patients for at least 1 hour after injections.

REGEN-COV may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion or hypersensitivity reactions, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

Health care professionals should obtain product-specific information pertaining to emergency use by referring to Regeneron's EUA website and directly accessing the FDA Emergency Use Authorization Letter, Dear Healthcare Provider letter, and HCP and patient fact sheets.

Coding and Reimbursement Information
Although REGEN-COV is being distributed at no cost during the initial Emergency Use Authorization, providers may seek reimbursement for the treatment administration using the appropriate drug administration codes.

Regeneron has provided a general REGEN-COV Drug Administration Coding Reference Tool, available on regencov.com. It is important, however, that providers clarify and confirm any coding/billing requirements with respective payers.

Reporting Adverse Events

- The prescribing healthcare provider and/or the provider's designee are responsible for mandatory reporting of all medication errors and **ALL SERIOUS ADVERSE EVENTS** potentially related to REGEN-COV. These adverse events must be reported within 7 calendar days from the onset of the event
- Healthcare facilities and providers must report therapeutics information and demonstrate adequate utilization via data reported through HHS Protect, Teletracking or National Healthcare Safety Network (NHSN) as directed by the U.S. Department of Health and Human Services
- **MedWatch adverse event reports can be submitted to the FDA here, by submitting a postage-paid Form FDA 3500 and returning by mail/fax, or by calling 1-800-FDA-1088 to request a reporting form.** In addition, please provide a copy of all FDA MedWatch forms to Regeneron Pharmaceuticals, Inc via fax (1-888-876-2736) or email (medical.information@regeneron.com)

For any additional questions related to this notification, contact Regeneron Medical Information at 844-734-6643 or medical.information@regeneron.com.

[1] Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated
[2] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html
[3] Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html

Sincerely,

Aaron Franczek
Consultant
DK Pierce and Associates, Inc.
10910 Creek Way
Zionsville, IN 46077
(317) 873-0303
aaron.franczek@dkpierce.net