REGENERON
SCIENCE TO MEDICINE®

777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
914.847.7400

Dear Valued Healthcare Provider,

As you may have heard reported, monoclonal antibody treatment has been underutilized, according to many experts. For example, Health and Human Services Secretary Alex Azar stated he's been "very disappointed that this incredibly important tool that should be getting used more frequently [and] that should be getting used to keep people out of the hospital" isn't reaching more patients. "We simply can't have this very valuable tool sitting on the shelves," Azar said.[1]

In the face of this worsening national crisis and given the risk/benefit profile of Regeneron's investigational monoclonal antibody therapy, patients who are not currently hospitalized due to COVID-19 or on oxygen due to COVID-19, should be evaluated for treatment with casirivimab and imdevimab, consistent with the Emergency Use Authorization.

The U.S. Food and Drug Administration (FDA) has granted Emergency Use Authorization (EUA) for Regeneron's casirivimab and imdevimab, administered together, for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years and older weighing at least 40kg) with positive SARS-CoV2 viral testing who are at high risk for progressing to severe COVID-19 and/or hospitalization.

Note casirivimab and imdevimab are 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.

Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19.

We want to ensure you have all the information necessary to understand and discuss this treatment option with appropriate patients. As part of the recently granted EUA, Regeneron has developed educational materials on the use of casirivimab and imdevimab for healthcare providers, available at www.regeneroneua.com.

Within the above website and through the links below, please find resources, including:

Fact Sheet – Healthcare Provider
Fact Sheet - Patient
Dear Healthcare Provider Letter

777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
914.847.7400

Educational Vignettes:

Topics include:

- Packaging
- Preparation
- Passive vs. Active Immunity

Emergency Use Authorization Guidebook
FAQs

For additional questions, please reach out directly to Regeneron Medical Information at medical.information@regeneron.com or 1-844-734-6643.

We recognize there are numerous time demands and potential infrastructure challenges associated with antibody utilization. We are interested to discuss challenges and share best practices to better assist your efforts. We are filled with gratitude for your continued work on the front lines of this battle. Please be assured we remain committed to support you and your patients.

[1]Weintraub K. Monoclonal antibodies may have helped Donald Trump recover from COVID-19, but many others aren't getting them. *USA Today*. December 21, 2020. Accessed January 11, 2021. https://www.usatoday.com/story/news/health/2020/12/21/monoclonal-antibodies-covid-19-donald-trump-regeneron-lilly/3895201001/

777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
914.847.7400

Casirivimab and Imdevimab Authorized Use and Safety Information

Casirivimab and imdevimab, to be administered together, are authorized for use for the treatment of mild to moderate coronavirus disease for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults 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 progressing to severe COVID-19 and/or hospitalization. Casirivimab and imdevimab are not FDA-approved for these uses and are authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of casirivimab and imdevimab under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Limitations of Authorized Use

- Casirivimab and imdevimab are 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.

- Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19.

Dosing and Administration

The recommended dose of casirivimab and imdevimab under the EUA is 1200 mg of casirivimab and 1200 mg of imdevimab administered as **a single intravenous (IV) infusion over at a maximum rate of 250mL/hr.**

The optimal dosing regimen for treatment for COVID-19 has not yet been established. The recommended dosing regimen may be updated as data from clinical trials becomes available.

CASIRIVIMAB AND IMDEVIMAB MUST BE ADMINISTERED TOGETHER AFTER DILUTION BY INTRAVENOUS (IV) INFUSION ONLY.

Casirivimab and imdevimab solutions must be diluted prior to administration.

Casirivimab and imdevimab should be given together as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset. For more information on high risk patients, please view the **HCP fact sheet**.

777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
914.847.7400

Note that casirivimab and imdevimab carton and vials may instead be labeled **REGN10933** and **REGN10987** respectively.

IMPORTANT SAFETY INFORMATION

Casirivimab and imdevimab are unapproved investigational therapies and there are limited clinical data available. Serious and unexpected adverse events may occur that have not been previously reported with casirivimab and imdevimab use.

Warnings and Precautions

Hypersensitivity Reactions Including Anaphylaxis and Infusion-Related Reactions: There is a potential for serious hypersensitivity reaction, including anaphylaxis, with administration of casirivimab and imdevimab. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care. Infusion-related reactions have been observed with administration of casirivimab and imdevimab. Signs and symptoms of infusion related reactions may include fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and/or dizziness. If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19: Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, casirivimab and imdevimab are 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:

Serious adverse events (SAEs) were reported in 4 (1.6%) patients in the casirivimab and imdevimab 2,400 mg group, 2 (0.8%) patients in casirivimab and imdevimab 8,000 mg group and 6 (2.3%) patients in the placebo group. None of the SAEs were considered to be related to study drug. SAEs that were reported as Grade 3 or 4 adverse events were pneumonia, hyperglycemia, nausea and vomiting (2,400 mg casirivimab and imdevimab), intestinal obstruction and dyspnea (8,000 mg casirivimab and imdevimab) and COVID-19, pneumonia and hypoxia (placebo). **Casirivimab and imdevimab are not authorized at the 8,000 mg dose (4,000 mg casirivimab and 4,000 mg imdevimab).**

One anaphylactic reaction was reported in the clinical program. The event began within 1 hour of completion of the infusion, and required treatment including epinephrine. The event resolved. Infusion-related reactions, of grade 2 or higher severity, were reported in 4 subjects (1.5%) in the 8,000 mg (4,000 mg casirivimab and 4,000 mg imdevimab) arm. These infusion-related reactions events were moderate in severity; and include pyrexia, chills, urticaria, pruritus, abdominal pain, and flushing. One infusion-related reaction (nausea) was reported in the placebo arm and none were reported in the 2,400 mg (1,200 mg casirivimab and 1,200 mg imdevimab) arm. In two subjects receiving the 8,000 mg dose of casirivimab and imdevimab, the infusion-related reactions

777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
914.847.7400

(urticaria, pruritus, flushing, pyrexia, shortness of breath, chest tightness, nausea, vomiting) resulted in permanent discontinuation of the infusion. All events resolved.

Patient Monitoring Recommendations: Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

Adverse Reactions and Medication Errors Reporting Requirements

The prescribing healthcare provider and/or the provider's designee are responsible for mandatory reporting of all medication errors and **ALL SERIOUS ADVERS EVENTS** potentially related to casirivimab and imdevimab. These adverse events must be reported within 7 calendar days from the onset of the event.

MedWatch adverse event reports can be submitted to the FDA online here, by using 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 or email.

Use in Specific Populations:

Pregnancy: There is currently limited clinical experience in the use of casirivimab and imdevimab in COVID-19 patients who are pregnant. Casirivimab and imdevimab therapy should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

Nursing Mothers: There is currently no clinical experience in the use of casirivimab and imdevimab in COVID-19 patients who are breastfeeding. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for casirivimab and imdevimab and any potential adverse effects on the breastfed child from casirivimab and imdevimab or from the underlying maternal condition.