Emergency Use Authorization (EUA) for
casirivimab and imdevimab
Center for Drug Evaluation and Research (CDER) Review

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)	000091
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Regeneron Pharmaceuticals, Inc. Yunji Kim, PharmD Director, Regulatory Affairs Regeneron Pharmaceuticals, Inc. Email: yunji.kim@regeneron.com
Manufacturer	Regeneron Pharmaceuticals, Inc.
Submission Date(s)	January 26, 2021 (eCTD#0047) March 23, 2021 (eCTD#0077)
Receipt Date(s)	January 26, 2021 (eCTD#0047) March 23, 2021 (eCTD#0077)
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Proprietary Name	REGEN-COV
Established Name/Other names used during development	casirivimab (REGN10933) and imdevimab (REGN10987)
Dosage Forms/Strengths	SEE ATTACHED ADDENDUM
Therapeutic Class	SARS-CoV-2 spike protein directed human IgG1 monoclonal antibodies (mAbs)
Intended Use or Need for EUA	Mild to moderate coronavirus disease 2019 (COVID-19)
Intended Population(s)	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 progressing to severe COVID-19 and/or hospitalization

I. Introduction

This review summarizes the changes related to the high risk criteria in the Health Care Provider Fact Sheets (HCP FS) for EUA 091.

On November 21, 2020, the Agency issued EUA 091 for REGEN-COV for the treatment of mild to moderate COVID-19 in adult and pediatric patients (12 years of age 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. The high risk criteria in the HCP FS are as follows:

- Have a body mass index (BMI) ≥35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥65 years of age
- Are ≥55 years of age AND have
  - cardiovascular disease, OR
  - hypertension, OR
  - chronic obstructive pulmonary disease/other chronic respiratory disease.
- Are 12 – 17 years of age AND have
  - BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm, OR
  - sickle cell disease, OR
  - congenital or acquired heart disease, OR
  - neurodevelopmental disorders, for example, cerebral palsy, OR
  - a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
  - asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

In response to requests from prescribers and community stakeholders, the Applicant proposed broadening the high risk criteria to allow treatment of outpatients who meet any high risk medical conditions and factors identified by the Centers of Disease Control and Prevention (CDC) and which are not covered in the EUA FS. The Division agreed that such a proposal was reasonable based on phase 3 results and high risk subgroup analyses from the ongoing outpatient treatment trial, R10933-10987-COV-2067 (NCT04425629). Phase 3 results from COV-2067 were submitted to EUA 091 in March 2021. These data form the basis for revising the EUA high risk criteria for patient eligibility for treatment with REGEN-COV.

II. Data Supporting Revision of EUA High Risk Criteria

COV-2067 is a phase 1/2/3, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of REGEN-COV in outpatients (non-hospitalized) with SARS-CoV-2 infection. In phase 3 Cohort 1, eligible adult patients were randomized 1:1:1 to receiving a single single intravenous dose of placebo or REGEN-COV 2400 mg IV (1200 mg of casirivimab and 1200 mg of imdevimab) or REGEN-COV 1200 mg IV (600 mg of casirivimab and 600 mg of imdevimab).

SEE ATTACHED ADDENDUM

The phase 3 protocol-defined risk factors were broader than those in the EUA HCP FS, and included the following: age ≥50 years; BMI ≥30 kg/m^2;

cardiovascular disease, including hypertension; chronic lung disease, including asthma; type 1 or type 2 diabetes mellitus; chronic kidney disease, including those on dialysis; chronic liver disease; or immunosuppressed, based on investigator's assessment [examples include cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anemia, thalassemia, and prolonged use of immune-weakening medications].

The primary efficacy endpoint is the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through Day 29. The efficacy analyses were conducted on the modified full analysis set (mFAS) which included all randomized patients with a positive central-lab-determined RT-qPCR test from nasopharyngeal swab samples at randomization and with at least one risk factor, at baseline, for severe COVID-19.

COVID-19-related hospitalization or all-cause deaths were observed in fewer patients in the REGEN-COV group compared to placebo (71.3% relative risk reduction, 95% confidence interval 52, 83; p<0.0001). The number needed to treat to prevent one COVID-19-related hospitalizion or all-cause mortality was 30 (95% CI 21, 48).

III. Assessment

Based on the totality of scientific information available, we believe that revising the current definition of "high risk" for the purposes of EUA 091 to include the additional groups deemed by the CDC to be at high risk for severe COVID-19 is both scientifically appropriate[1] and necessary for the public health. Our assessment considered the following:

- A clinically and statistically significant reduction in COVID-19 hospitalization and all-cause deaths was observed with the authorized dose compared to placebo.
- A trend for reduction in COVID-19 hospitalization or all-cause deaths with REGEN-COV compared to placebo in individual high risk subgroups. In some of the high risk subgroups, the number of events was too small to form definitive conclusions; and the trial was not powered to assess differences for individual subgroups or in subgroup of patients with more than one high risk condition. However, the favorable overall benefit-risk as well as consistent favorable trends in individual high risk subgroups strongly support expanding criteria to allow treatment of patients with risk factors identified by the CDC, including those that were not studied directly in the context of this clinical trial.

[1] FDA has determined that the totality of scientific evidence available supporting the relevant revisions to the authorized labeling described in the memorandum satisfies the EUA criteria under section 564(c) of the Federal Food, Drug and Cosmetic Act.

- Given that the antiviral mechanism of action is independent of the specific risk factor or medical condition, it is expected that patients with any risk factor for severe COVID-19 could potentially derive benefit from treatment with monoclonal antibodies directed against the virus.
- Separately, we note that CDC's categorization of conditions that confer high risk of hospitalization or death from COVID-19 have evolved since the pandemic began and the available clinical data are for high risk subgroups as defined by the CDC at the time of trial initiation and conduct.
- It is possible that CDC's definition of high risk will get updated, in the future, with other medical conditions or get modified with emerging information about the disease. For this reason, we determined that broadening of high risk criteria in our Fact Sheet should be accompanied by the link to the appropriate CDC webpage https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. This CDC website provides a comprehensive list of high risk conditions that we anticipate would get updated in real time, should the CDC identify additional conditions in the future or modify existing ones.

Additional groups deemed by CDC to be at high risk for severe COVID-19 will stand to benefit with this FS revision. Treating additional high risk subgroups is beneficial to individual patients and will have a broader beneficial impact on U.S. public health.

IV. Regulatory Conclusion

Based on the totality of scientific evidence available, the Division has determined that the known and potential benefits of REGEN-COV outweigh the known and potential risks for outpatients who have underlying high risk medical conditions or factors identified by the CDC.

The Division discussed broadening the high risk criteria in the FS including the revised list of high risk conditions and CDC webpage link with other US Government agencies including the Office of Assistant Secretary of Preparedness and Response (ASPR), CDC, and the NIH COVID-19 Treatment Guidelines Panel.

V. Summary of Revisions to EUA Fact Sheets

- **The Box and Section 2.1 in the HCP Fact Sheet** were revised to list the broadened definition of high risk conditions and include the webpage link to the CDC website as shown below:

  The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example age ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of REGEN-COV under the EUA is not limited to the conditions listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

- **The Fact Sheet for Patients, Parents and Caregivers** was revised to reflect the expanded high risk criteria. These changes are shown, below, in bold:

  COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your other medical conditions to become worse. People of all ages with severe, long-lasting (chronic) medical conditions like heart disease, lung disease, and diabetes, for example, **and other conditions including obesity**, seem to be at higher risk of being hospitalized for COVID-19. **Older age, with or without other conditions, also places people at higher risk of being hospitalized for COVID-19.**

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHARU J MULLICK
05/14/2021 03:12:04 PM

MARY E SINGER
05/14/2021 03:14:13 PM

CLINICAL REVIEW
US FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFECTIOUS DISEASES
DIVISION OF ANTIVIRALS
ADDENDUM

EUA:	000091
Product:	REGN10933 and REGN10987 (casirivimab and imdevimab)
Sponsor:	Regeneron Pharmaceuticals, Inc.
Intended Use:	Mild to moderate coronavirus disease 2019 (COVID-19)
Intended Population:	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 progressing to severe COVID-19 and/or hospitalization

---

This addendum is for corrections to the clinical review for EUA 91 eCTD #0047 and eCTD #0077, dated May 14, 2021, which supported the reauthorization of EUA 91 Fact Sheets.

The corrections do not alter the conclusion of the clinical review for EUA 91. The corrections do not alter the information in the approved EUA Healthcare Provider and Patient Fact Sheets.

The corrections are as follows:

- On Page 1, Dosage Forms/Strengths in the table corrected to “1200 mg intravenous (IV) casirivimab and 1200 mg IV imdevimab”,

- On Page 2, Section II Data Supporting Revision of EUA High Risk Criteria, minor editorial change to delete the repeated word, “single”.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NINA MANI
05/27/2021 09:20:35 AM

CHARU J MULLICK
05/27/2021 09:38:37 AM

MARY E SINGER
05/27/2021 09:40:15 AM