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)
Receipt Date(s)	January 26, 2021 (eCTD#0047)
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	1200 mg intravenous (IV) casirivimab and 1200 mg IV imdevimab
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. Summary of Revisions to EUA Health Care Provider Fact Sheet (FS) and Patient FS

A) Summary of Revisions to EUA Health Care Provider Fact Sheet (FS)

- **Updated the Box and Microbiology/Resistance Section 15** to communicate that healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area when considering treatment options, and to provide susceptibility data for current variants of concern.

  SARS-CoV-2 is evolving over time, resulting in genetic variation in the population of circulating viral strains. Some variants can cause resistance to one or more of the monoclonal antibody therapies authorized to treat COVID-

19. Since the authorization of EUA 91, viral variants of SARS-CoV-2 have been noted to be circulating in the United States. In response, the Division requested that Regeneron conduct cell culture neutralization studies to assess the activity of casirivimab and imdevimab together against these variants, and/or amino acid substitutions found in these variants. The Applicant provided pseudovirus data for spike protein substitutions found in variants B.1.1.7 (UK origin), B.1.351 (South Africa origin), P.1 (Brazil origin), B.1.427/B.1.429 (California origin), and B.1.526 (New York origin). Following review of the data indicating that casirivimab and imdevimab together would likely retain activity against the circulating variants of interest and variants of concern, changes were made to the Healthcare Provider Fact Sheet to inform healthcare providers of these results

The pseudovirus susceptibility data provided by the Applicant were updated in the text in the Antiviral Resistance Subsection of Section 15. A Table (shown below) was added summarizing the pseudovirus data for key substitutions found in these variants. A sentence was added after this Table to indicate that it is not known how pseudovirus data correlate with clinical outcomes.

Table 1: Pseudovirus Neutralization Data for SARS-CoV-2 Variant Substitutions with Casirivimab and Imdevimab Together

Lineage with Spike Protein Substitution	Key Substitutions Tested	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y[a]	no change[c]
B.1.351 (South Africa origin)	K417N, E484K, N501Y[b]	no change[c]
P.1 (Brazil origin)	K417T + E484K	no change[c]
B.1.427/B.1.429 (California origin)	L452R	no change[c]
B.1.526 (New York origin)[d]	E484K	no change[c]

[a] Pseudovirus expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.

[b] Pseudovirus expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, A701V.

[c] No change: <2-fold reduction in susceptibility.

[d] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

Given the importance of the information, the following language was added to the Box with reference to Section 15 for details.

Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. Health care providers should review the Antiviral Resistance information in Section 15 of this Fact Sheet for details regarding specific variants and resistance, and refer to the CDC website (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html) as well as information from state and

local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

- **Updated Dose Preparation and Administration Section 2.4** with minimum infusion times and preparation instructions for additional sizes of prefilled 0.9% sodium chloride infusion bag sizes specifically, 50 ml, 100 ml, and 150 ml bag sizes. The revisions were made in response to interest expressed by healthcare providers in the field for convenient administration and faster infusion rates. The Applicant provided clinical safety information and nonclinical information to support the revisions (refer to Section II for details). Overall, the revisions allow for reduced infusion administration time ranging from 20 minutes to 52 minutes, depending on the size of the sodium chloride infusion bag.

- **Updated Adverse Reactions and Medication Errors Reporting Requirements and Instructions Section 8:** Minor change made to align the language for reporting of adverse events or medication errors to MedWatch, "REGEN-COV use for COVID-19 under Emergency Use Authorization (EUA)", with the language in the Letter of Authorization[1].

B) Summary of Revisions to EUA Patient FS

- Updated "HOW WILL I RECEIVE REGEN-COV (casirivimab and imdevimab)?" to specify the infusion administration time is 20 to 52 minutes, or longer, as determined by the healthcare provider.

II. FDA Assessment to Support Revisions to HCP FS Section 2.4

Previously, the HCP FS allowed for use of the 250 ml sodium chloride infusion bag and a minimum infusion time of at least 60 minutes. The revisions allow for reduced infusion administration times with the minimum infusion time ranging from 20 minutes to 52 minutes, depending on the size of the sodium chloride infusion bag. Options for use of 50 ml, 100 ml, and 150 ml sodium chloride infusion bags were added, as shown in the table below.

[1]Refer to the Letter of Authorization for EUA 91 reissued on February 25, 2021

Table 2: Recommended Dosing, Dilution and Administration Instructions for Casirivimab with Imdevimab for IV Infusion

Casirivimab with Imdevimab 2,400 mg Dose[a]. Add: • **10 mL of casirivimab (use 1 vial of 11.1 mL OR 4 vials of 2.5 mL) and** • **10 mL of imdevimab (use 1 vial of 11.1 mL OR 4 vials of 2.5 mL)** **for a total of 20 mL into a prefilled 0.9% sodium chloride infusion bag and administer as instructed below[b]**		
Size of Prefilled 0.9% Sodium Chloride Infusion Bag	**Maximum Infusion Rate**	**Minimum Infusion Time**
50 mL[c]	210 mL/hr	20 minutes
100 mL	310 mL/hr	23 minutes
150 mL	310 mL/hr	33 minutes
250 mL	310 mL/hr	52 minutes

[a] 1,200 mg casirivimab and 1,200 mg imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.
[b] After infusion is complete, flush with 0.9% Sodium Chloride Injection
[c] The minimum infusion time for patients administered casirivimab with imdevimab together using the 50 mL prefilled 0.9% Sodium Chloride infusion bag must be at least 20 minutes to ensure safe use.

The revisions were based on the available clinical safety data and product quality data, outlined below:

Product quality

The available compatibility data support that the maximum infusion rate of 310 mL per hour, using 0.9% sodium chloride as diluent, does not adversely impact product quality (refer to the Quality Review memo dated March 1, 2021 for additional details). The compatibility studies evaluated relevant critical quality attributes of the product before and after passage through multiple types of infusion sets. The infusion rates provided in Table 2 are well within the ranges tested in compatibility studies for multiple infusion sets. Therefore, the infusion rates for each infusion bag are acceptable from product quality perspective. Information provided to the EUA support that available prefilled sodium chloride infusion bags of 50 mL, 100 mL, 150 mL, and 250 mL volumes have sufficient maximum additive volume in the bag to accommodate the addition of 20 mL of the drug product (10 mL of casirivimab and 10 mL of imdevimab). In addition, the combined maximum potential endotoxin contribution of the infusion solution and the drug product included in Table 2 is within the USP endotoxin threshold for the intended population.

Clinical

Safety data available for the 8000 mg dose (4000 mg of each mAb) administered over approximately 60 minutes, which corresponds to an infusion rate of 133 mg of protein/minute, supports administration of the authorized 2400 mg dose (1200 mg of each mAb) at faster infusion rates. Overall, a low rate of infusion related reactions (IRR) was observed in the 2400 mg IV and 8000 mg IV treatment groups in the outpatient treatment trial, R10933-10987-COV-2067, and the inpatient treatment trial, R10933-10987-COV-2066, which supported the revised infusion rates.

- R10933-10987-COV-2067 – In the phase 1 and 2 analysis, IRRs were observed in 1.5%, zero, and 0.4% of subjects in the 8000 mg, 2400 mg, and the placebo arms, respectively. In the blinded data from the ongoing portion of this trial (n=5043), the overall infusion rate was 0.2%.

- R10933-10987-COV-2066 – In the phase 1 and 2 analysis in Cohort 1 (patients requiring low flow oxygen at randomization), IRRs were observed in 3.1%, 1.8%, and 1.8% of subjects in the 8000 mg, 2400 mg, and the placebo arms, respectively. In the phase 1 and 2 analysis in Cohort 2 (patients requiring high flow oxygen at randomization) and Cohort 3 (patients on mechanical ventilation at randomization), no IRRs were observed.

In addition, the optimal infusion rate was determined by clinically acceptable infusion rates for the administration of protein in normal saline volume based on actual clinical experience, as well as discussions with Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response about operational feasibility with product administration in the field setting.

III. Regulatory Conclusions

FDA is working closely with the sponsors of the mAb EUAs to understand the potential impact of a variant on the effectiveness of the currently authorized mAb therapies. FDA is also working with the Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response, the CDC, and other government organizations to closely monitor the situation. Based on the available data, revisions were made to the Fact Sheet for Healthcare Providers to provide updates to the antiviral resistance information as detailed above.

FDA agrees with the addition of different sizes of 0.9% Sodium Chloride infusion bags and proposed infusion times based on both safety and compatibility data to provide additional flexibility to providers for the administration of REGEN-COV. The Fact Sheet for Healthcare Providers was also revised to provide updated minimum infusion time for product administration and to provide updated

preparation instructions for additional sizes of prefilled 0.9% Sodium Chloride infusion bag sizes specifically, 50 ml, 100 ml, and 150 ml bag sizes. These revisions were based on acceptable clinical safety and product quality information, as well as discussions with Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response about operational feasibility with product administration in the field setting.

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/s/

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