

**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. Mobile: (b) (6) Email: yunji.kim@regeneron.com
Manufacturer	Regeneron Pharmaceuticals, Inc.
Submission Date(s)	January 21, 2021 (HCP FS) & January 23, 2021 (DHCP Letter)
Receipt Date(s)	January 21, 2021 (HCP FS) & January 23, 2021 (DHCP Letter)
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 test and who are at high risk for progressing to severe COVID-19 and/or hospitalization

I. Summary of Revisions to EUA Letter of Authorization

- Updated with the proprietary name 'REGEN-COV'.
- Added information about REGEN-COV dose pack, a new packaging presentation.
- Made revisions to the condition on requesting future changes to the authorization, including changes to the authorized Fact Sheets, and added new conditions relating to the development of instructional or educational

materials as well as certain mandatory reporting requirements for healthcare facilities and providers.

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

- **Proprietary name ‘REGEN-COV’ added:** The name ‘REGEN-COV’¹ replaced ‘casirivimab and imdevimab’ throughout the FS, except in specific sections where referring to the individual monoclonal antibody by name is necessary or to provide clarification that REGEN-COV denotes the two monoclonal antibodies, casirivimab and imdevimab.
- **Warnings Section 5:** updated with safety events of concern identified in safety narratives and summaries submitted by the Applicant as well as FAERS cases that were reported with product use under EUA².
 - **Subsection 5.1 “Hypersensitivity Reactions including Anaphylaxis and Infusion-Related Reactions” was updated** with the following signs and symptoms of infusion-related reactions: “difficulty breathing, reduced oxygen saturation, fatigue, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), altered mental status, hypertension, diaphoresis”.
 - **Subsection 5.2 “Clinical worsening after REGEN-COV administration” was added** to communicate that clinical worsening of COVID-19 after administration of REGEN-COV is reported, the causality assessment, and that some events required hospitalization, as follows: “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. It is not known if these events were related to REGEN-COV use or were due to progression of COVID-19.”

III. Summary of Revisions to EUA Patient FS

- The name ‘REGEN-COV’ was added to the Patient FS.
- Section “WHAT ARE THE IMPORTANT POSSIBLE SIDE EFFECTS?” was updated with descriptions for side-effects of allergic reactions. This section was also updated to include a separate bulleted subsection for

¹Refer to the Proprietary Name review in DARRTS under IND 148069 dated 01/19/2021 by Division of Medication Error Prevention and Risk Management (DMEPA), Office of Surveillance and Epidemiology

²Refer to the clinical review in DARRTS under IND 148069 dated 02/02/2021 by the Division of Antivirals (DAV) clinical review team

“Worsening symptoms after treatment” including descriptions of side-effects of clinical worsening.

IV. Summary of EUA Dear Health Care Provider (DHCP) Letter

- **Provides the proprietary name ‘REGEN-COV’.**
- **Communicates new packaging as REGEN-COV dose pack:**
 - The letter provides a description of the REGEN-COV dose pack including images of what healthcare providers should expect. REGEN-COV dose pack is a plastic bag that contains cartons of casirivimab and imdevimab to make one 2,400 mg dose (1,200 mg of casirivimab and 1,200 mg of imdevimab) and a one-page informational document. Depending on vial size, the dose pack may have different numbers of cartons (2, 5, or 8) each containing a vial containing casirivimab or imdevimab to make a single treatment dose.

Based on the updates above, namely the updates to the EUA-related documents to incorporate the proprietary name and the details on the authorized product as a dose pack bag, as well as to require additional reporting, FDA will be re-issuing the Letter of Authorization for EUA 91 to protect the public health or safety under section 564(g)(2) of the FD&C Act.

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

IND: 148069 SDN 225
Date received: 1/15/2021
Date review completed: 1/22/2021
Sponsor: Regeneron Pharmaceuticals, Inc.
Product: REGN10933 and REGN10987 (casirivimab and imdevimab)
Class: Antiviral; anti-spike SARS-CoV-2 monoclonal antibodies
Indication: Treatment and Prevention of COVID-19
Subject: Safety narratives from hospitalized patients Trial COV-2066
Reviewer: Charu Mullick MD – Clinical Reviewer
Mary Singer MD PhD – Clinical Team Leader

This review provides a summary and assessment for hypersensitivity reactions (HSR), respiratory decompensation events, and neuropsychiatric events in trial R10933-10987-COV-2066 (hereafter referred to as COV-2066). This submission is provided in response to the Division's request brief narratives from COV-2066 for serious hypersensitivity reactions including anaphylaxis and serious infusion related reactions, brief narratives for events related to acute respiratory decompensation or psychiatric events during or within 2 hours of infusion including delirium and confusion. Ten cases were identified in the unblinded data from Cohorts 1, 2, and 3 in the phase 2 analysis dataset in COV-2066. Based on these cases and FAERS reports from use under Emergency Use Authorization, we recommend safety-related revisions to the Healthcare Provider Fact Sheet for EUA 91.

Submission summary

Trial COV-2066 is a phase 1/2/3 randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of REGN10933 and REGN10987 in hospitalized patients with COVID-19. Originally, participants were enrolled into one of four cohorts, depending on the oxygen requirements at randomization. Within each cohort, participants are randomized 1:1:1 to 2400 mg IV REGEN-COV or 8000 mg IV REGEN-COV or placebo.

- Cohort 1A: symptomatic but not requiring supplemental oxygen
- Cohort 1: oxygen saturation >93% on low-flow oxygen via nasal cannula, simple face mask, or similar device
- Cohort 2: Requiring high-intensity oxygen therapy, but not on mechanical ventilation
- Cohort 3: Requiring mechanical ventilation

In October 2020, the Sponsor notified the Division of the recommendation from the trial's Independent Data Monitoring Committee (IDMC) to pause enrollment in Cohorts 2 and 3 for safety reasons. The IDMC recommended continued enrollment in the remaining cohorts in COV-2066 and in other trials.

In December 2020, the Sponsor unblinded data for Cohorts 1, 2, and 3 from 867 patients who were randomized on or before December 1, 2020. In this unblinded dataset, 10 cases met the Division's request. In 6 of the 10 cases, the patient developed worsening of respiratory status during or within 2

hours after the end of the infusion (refer to cases #5-10 in Table 1 in the Appendix). Two cases of the adverse event (AE) of chills were reported (case #1, 2). Two cases of anxiety AE (# 4, 5), and one case of anaphylactic reaction (#3) were included in the 10 identified cases.

1. Worsening of respiratory status

In 6 cases, the patient developed worsening of respiratory status during administration of the REGEN-COV infusion or within 2 hours after the end of the infusion. The specific AEs were acute respiratory distress syndrome (n=2), hypoxia (n=2), COVID-19 (n=1), hypoxia (n=1), and dyspnea (n=1). The events began during infusion administration in 3 cases, and within two hours after infusion end in the remaining three cases. In 4 cases, the event occurred in the setting of fluctuating and tenuous pulmonary status with patients requiring high-flow oxygen or invasive mechanical ventilation prior to start of the infusion. Increasing oxygen requirements were attributed by the investigator to ARDS, or progression of COVID-19, or pulmonary embolism. In 5 of the 6 cases, the investigator assessed the AE to be unrelated to the infusion. In one case, #5, the episode of dyspnea accompanied by anxiety was assessed as related to study treatment.

Overall, the timing of onset of these events, either during or within 2 hours of infusion end, raises potential concern about a possible drug effect. As such, it is difficult to distinguish drug effect from progression of underlying COVID-19 or complications of COVID-19 (e.g., pulmonary embolism). To communicate the possible drug effect resulting in worsening clinical status, we recommend addition of the language to convey the risk in the Healthcare Provider Fact Sheet for EUA 91. The specific language recommended for the Fact Sheet, shown below, takes into consideration the findings from above cases as well as additional AEs reported in FAERS from product use under EUA.

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. It is not known if these events were related to REGEN-COV use or were due to progression of COVID-19.

2. Anaphylactic reaction

The AE of anaphylactic reaction in one patient is described in the current version of HCP Fact Sheet (the case was identified by the clinical review team during review of EUA 91). No specific change in the HCP Fact Sheet is recommended based on additional case information provided in this submission.

3. Neuropsychiatric events

SEE ATTACHED ADDENDUM

Two cases of chills were reported; these were grade 4 in severity and both events were assessed by the investigator to be related to the infusion. It is notable that both events occurred in severely ill patients who were on invasive mechanical ventilation before the infusion was started. Chills is included in the current version of the HCP Fact Sheet as one of the presenting signs of infusion-related reaction; therefore, no specific change to the Fact Sheet is currently recommended.

Two cases of anxiety were reported; these AEs were grade 1 or 2 in severity; both AEs were assessed by the investigator to be related to the infusion. As these anxiety AEs were not grade 3 or 4 in severity, no specific change is recommended to the HCP Fact Sheet based on the cases.

Assessment

Based on the submitted information as well as FAERS cases that were reported with product use under EUA, as provided to DAV by DPV/OSE, we recommend the following edits to the Warnings section of the Healthcare Provider Fact Sheet for EUA 91.

- Subsection 5.1 “Hypersensitivity Reactions including Anaphylaxis and Infusion-Related Reactions” should be updated with the following signs and symptoms of infusion-related reactions: “difficulty breathing, reduced oxygen saturation, fatigue, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), altered mental status, hypertension, diaphoresis”.
- Subsection 5.2 “Clinical worsening after REGEN-COV administration” should be added to communicate that clinical worsening of COVID-19 after administration of REGEN-COV is reported, and the causality assessment, as follows: “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. It is not known if these events were related to REGEN-COV use or were due to progression of COVID-19.”

The Patient Fact Sheet section “WHAT ARE THE IMPORTANT POSSIBLE SIDE EFFECTS?” should be updated with descriptions for side-effects of allergic reactions and to include a separate bulleted subsection for “Worsening symptoms after treatment” including descriptions of side-effects of clinical worsening.

ID #	Age/ Gender/ Cohort/ Dose	Preferred AE term	Severity (grade)	Onset related to infusion	Treatment discontinuation /AE outcome	Investigator relatedness to infusion	Pertinent case information
1	84 M/ Cohort 3 2.4 gm	Chills, encephalopathy	4, 4	40 minutes after start	Infusion stopped. Chills resolved	Related	The patient, on mechanical ventilation, developed chills and rigors, indicative of seizure 40 minutes after the start of the infusion. Infusion was stopped; corrective treatment included lorazepam, levetiracetam, etomidate. EEG performed on the following days showed no seizure activity; MRI of the brain showed encephalopathy.
2	43 M/ Cohort 3/ 2.4 gm	Chills	4	57 minutes after start	Infusion stopped. AE resolved	Related	Patient with multiple comorbidities including end-stage renal disease. Patient was intubated in the hour preceding the start of the infusion. Nurse noted rigors or seizure 57 minutes after the infusion was started. Infusion was stopped. The neurologist assessed that the shaking was more consistent with rigors and did not appear tonic or clonic seizure. Shaking episodes continued until the next day. Corrective treatment with sedation and paralyzed (the patient was intubated at baseline).
3	63 M/ Cohort 2/ 8 gm	Anaphylactic reaction	4	59 minutes after end	N/A AE resolved	Related	Identified during EUA review – labeled in the HCP FS. Patient on high flow oxygen at baseline. Developed hypoxia (no hypotension) about an hour after the infusion ended. He was placed on BIPAP and transferred to the ICU. Received epinephrine, diphenhydramine, furosemide. Returned to baseline oxygenation status on the next day.
4	65 F/ Cohort 1 8 gm	Anxiety, flushing	1, 1	6 minutes after start	Infusion stopped. AE resolved	Related, Related	-
5	29 F/ Cohort 1/ 8 gm	Anxiety, dyspnea	2, 2	1 hour 9 minutes after end	N/A Resolved	Related, Related	Vital signs were not obtained during the episode of anxiety and dyspnea. No increase in supplemental oxygen requirement. Corrective treatment included alprazolam, methylprednisone, salbutamol, diphenhydramine, and ranitidine. Events resolved on the same day.
6	70 M/ Cohort 2/ 8 gm	COVID-19	3	100 minutes after start	Infusion was completed. AE resolved.	Not related	Worsening hypoxia started while infusion was being administered. Oxygen flow rate was increased, and the condition stabilized. Infusion was completed.
7	67 M/ Cohort 2/ 2.4 gm	ARDS	4	1 hour 35 minutes after end	N/A Resolved	Not related	Patient reported to develop ARDS about 1.5 hours after the infusion ended, requiring intubation. A complicated hospital course ensued including sepsis, MRSA lung infection, acute kidney injury. Eventual improvement and extubated by day 29.
8	61 M Cohort 3/ 8 gm	Hypoxia	5	5 minutes; infusion was resumed	Infusion resumed. Resolved	Not related	At baseline, the patient had low oxygen saturation (69%) on 4L oxygen. As soon as the infusion started, the patient became tachypneic and oxygen increased to 10 L. Infusion was paused. The patient was placed on a non-rebreather mask 15L. An hour later, once the condition stabilized, the infusion was resumed at 50% of the original infusion rate and completed without issue.
9	43 F/ Cohort 2/ 8 gm	ARDS	4	27 minutes after end	N/A Resolved	Not related	Patient on BIPAP with tenuous oxygen status at baseline and increasing O2 requirements just before the infusion was started. Both BP and O2 saturation dropped during the infusion, requiring mechanical ventilation. The patient went on to develop complications – MRSA bacteremia, ventilation associated pneumonia, small bowel obstruction and septic shock; and ultimately recovered.
10	88 F/ Cohort 1/ 8 gm	Hypoxia,	3	33 minutes after start	Infusion stopped. AE resolved	Not related	Hypoxia was attributed to multiple pulmonary emboli on CT scan and right leg deep vein thrombosis.

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**CLINICAL REVIEW
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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 test and who are at high risk for progressing to severe COVID-19 and/or hospitalization

This addendum is for a correction to the clinical review for IND 148069 SDN 225, dated February 2, 2021, page 2, Submission Summary, “3. Neuropsychiatric events.” This review supported the reauthorization of EUA 91 Fact Sheets (see clinical memo dated February 3, 2021).

The correction does not alter the efficacy and safety conclusion of the clinical review for IND 148069 SDN 225 or the conclusion for the memo for EUA 91. The correction does not alter the information in the approved EUA Healthcare Provider and Patient Fact Sheets.

The correction is as follows:

- Minor editorial change of sub-heading #3 “Neuropsychiatric events” to “Infusion-Related Reactions”

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