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

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)	000091
Date of Memorandum	December 22, 2021
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.
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	• 600 mg casirivimab and 600 mg imdevimab administered intravenously or subcutaneously as single dose • 300 mg casirivimab and 300 mg imdevimab administered intravenously or subcutaneously for repeat dosing at monthly intervals
Therapeutic Class	SARS-CoV-2 spike protein directed human IgG1 monoclonal antibodies (mAbs)
Intended Use or Need for EUA	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. 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 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) and o have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC) or o 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)
Intended Population(s)	Adult and pediatric patients (12 years of age and older weighing at least 40 kg)

Rationale and Revisions to EUA Fact Sheet

Antiviral Resistance Information in the Box and Section 15

On November 24, 2021, a new variant of SARS-CoV-2, B.1.1.529, was reported to the World Health Organization (WHO). On November 26, 2021, the WHO designated this variant as Omicron and classified it as a Variant of Concern (VOC). The first confirmed U.S. case of Omicron was identified on December 1, 2021. At present, there is uncertainty regarding the true prevalence of the Omicron variant and there is wide variability across the U.S. by region. On December 20, 2021, CDC posted surveillance data stating that Omicron accounted for 0.7% of the SARS-CoV-2 sequences for the week ending December 4, 2021. Nowcast modeling predicted that the frequency of the Omicron variant was 73.2% of the total circulating variants in the US for the week ending December 18, 2021, with a wide confidence interval (95% CI 34.0-94.9%).[1] Across the US, there are still regions where the Delta variant, against which REGEN-COV (casirivimab and imdevimab) retains activity, is still circulating with high frequency.

Pseudotyped VLPs expressing the spike protein from the B.1.1.529/BA.1 show reduced susceptibility to casirivimab alone, imdevimab alone, and casirivimab and imdevimab together; rendering the drugs unlikely to have activity against the Omicron variant.

As the rates of Omicron variant are likely to change rapidly over the coming weeks in different areas the United States, and in territories and U.S. jurisdictions, the language

[1] Source (accessed on 12/21/2021): https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fvariant-proportions.html#variant-proportions

related to SARS-CoV-2 Viral Variants in the boxed portion of the Healthcare Provider Fact Sheet has been modified and now directs health care providers to take variant frequency data into account when making treatment decisions and references other products that are available for use under emergency authorization. The language now reads:

- 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.
- There are other authorized treatments available and healthcare providers should choose an authorized therapeutic option with activity against the circulating variants in their state, territory, or US jurisdiction. Current variant frequency data are available at: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html
- For additional information on all products authorized for treatment or prevention of COVID-19, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

In addition, the following language has been added to Section 15:

> Casirivimab and imdevimab, individually (>1,732-fold and >754-fold, respectively) and together (>1,013-fold), demonstrated reduced neutralization activity against VLP pseudotyped with the full spike protein sequence of the B.1.1.529/BA.1 (Omicron; South Africa origin) lineage.

The information below, in red font, has been added to Table 9. Note that data for AY.1/AY.2 (Delta [+K417N]) and C.37 (Lambda) variants were removed as the sponsor identified errors in the sequences of the pseudotyped VLP used to test these; the changes are shown as strikethrough in the following table.

Table 1: Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Casirivimab and Imdevimab Together

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y[a]	no change[d]
B.1.351	South Africa	Beta	K417N+E484K+N501Y[b]	no change[d]
P.1	Brazil	Gamma	K417T+E484K+N501Y[c]	no change[d]
B.1.617.2/AY.3	India	Delta	L452R+T478K	no change[d]
~~AY.1/AY.2~~	~~India~~	~~Delta [+K417N]~~	~~K417N+L452R+T478K~~	~~no change~~
B.1.427/B.1.429	USA (California)	Epsilon	L452R	no change[d]
B.1.526[e]	USA (New York)	Iota	E484K	no change[d]
B.1.617.1/B.1.617.3	India	Kappa/no designation	L452R+E484Q	no change[d]
~~C.37~~	~~Peru~~	~~Lambda~~	~~L452Q+F490S~~	~~no change~~
B.1.621/B.1.621.1	Colombia	Mu	R346K+E484K+N501Y	no change[d]
B.1.1.529/BA.1	South Africa	Omicron	G339D+S371L+S373P+S375F+K417N+N440K, G446S+S477N+T478K+E484A+Q493R+G496S+Q498R+N501Y+Y505H[f]	>1,013-fold[g]

[a] Pseudotyped VLP 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] Pseudotyped VLP 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] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F.

~~[d] For AY.1: Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: (T19R, G142D, E156G, F157-, F158-, K417N, L452R, T478K, D614G, P681R, D950N).~~

[d] No change: ≤2-fold reduction in susceptibility.

~~[e] Commonly known as "Delta plus".~~

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

[f] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: A67V, del69-70, T95I, G142D/del143-145, del211/L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F

[g] Casirivimab and imdevimab together are unlikely to be active against variants from this lineage

Abbreviations: del, deletion; ins, insertion

The following language related to Omicron variant was also added in Section 15:

> Due to the large reduction of pseudotyped VLP neutralization activity against spike protein from the B.1.1.529/BA.1 (Omicron) variant, it is unlikely that casirivimab and imdevimab together will be active against this variant.

Use in Specific Populations – Section 11

Additional language was added to Section 11.1 regarding COVID-19 infection and pregnant individuals. It is now stated that "there are maternal and fetal

risks associated with untreated COVID-19 in pregnancy" and highlights the following clinical consideration:

> *Disease-associated maternal and/or embryo-fetal risk*
> COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Regulatory Conclusion

Given the dynamic nature of Omicron spread expected in the coming weeks across the different regions of the United States, and in territories and U.S. jurisdictions, changes to the Fact Sheet for Health Care Providers have been made to provide the most up to date information to health care providers. There may be circumstances, such as lower frequency of Omicron in a region, suspected infection with the Delta variant, and limited supply of alternative treatment options that retain activity against the Omicron variant, in which the use of REGEN-COV is clinically appropriate. FDA believes that the EUA standard is met for this product, including that the known and potential benefits of the product continue to outweigh the known and potential risks of the product because, among other factors, there remains significant uncertainty as to the specific prevalence of the Omicron variant in any particular state, territory, and U.S. jurisdiction at this time and there remains a need to make REGEN-COV (casirivimab and imdevimab) available for use given its activity against the Delta variant. Given the ongoing spread of the Omicron variant, FDA is continuing to evaluate whether additional changes to the scope of authorization and/or the Fact Sheet for Health Care Providers may be warranted in the coming weeks or months.

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