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	January 24, 2022
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

Brief Summary of Key Relevant Regulatory Actions for EUA 91

The EUA for REGEN-COV, casirivimab and imdevimab administered together, was initially authorized on November 21, 2020.

Circumstances have changed significantly since REGEN-COV was initially authorized. The first confirmed U.S. case of Omicron (B.1.1.529) was identified in December 2021 and the Omicron variant has subsequently become the dominant circulating variant across the U.S.[1] On December 22, 2021, the Fact Sheet for Health Care Providers was revised in Section 15 to provide pseudotyped virus data from the Omicron variant that showed reduced susceptibility to REGEN-COV, rendering REGEN-COV, when used according to the terms and conditions of the authorization at the time, unlikely to have activity against the Omicron variant. It's important to note that REGEN-COV is expected to retain activity against the Delta variant which was still widely circulating in December 2021.

Recommendation to Revise EUA 091

Consistent with section 564(g) of the Federal Food, Drug & Cosmetic Act, the Agency will periodically review the appropriateness and circumstances of each EUA. This provision further states, among other things, that the Secretary may revise an EUA if circumstances exist that make such revision appropriate to protect the public health or safety.

[1] Refer to Figure 1 below.

At the time of this review, the most recent surveillance data from actual sequencing on the CDC's website indicate that Omicron accounted for 89.1% (95%CI 86.1-91.7%) of the SARS-CoV-2 sequences nationally for the week ending January 1, 2022. CDC also uses available data to estimate the proportions of circulating variants in a model, called Nowcast, to enable timely public health action. Currently, Nowcast is our best tool to predict the prevalence of Omicron in real time. For the week ending January 15, 2022, Nowcast predicts that the frequency of the Omicron variant was 99.5% nationally, with a 95% prediction interval of 99.3-99.7% (see Figure 1 below).[2] All HHS regions[3] of the U.S. have point estimates above 95% for the Omicron variant.[4]

[2] Source (accessed on 1/22/2022): 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

[3] See https://www.hhs.gov/about/agencies/iea/regional-offices/index.html

[4] Source (accessed on 1/22/2022): 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

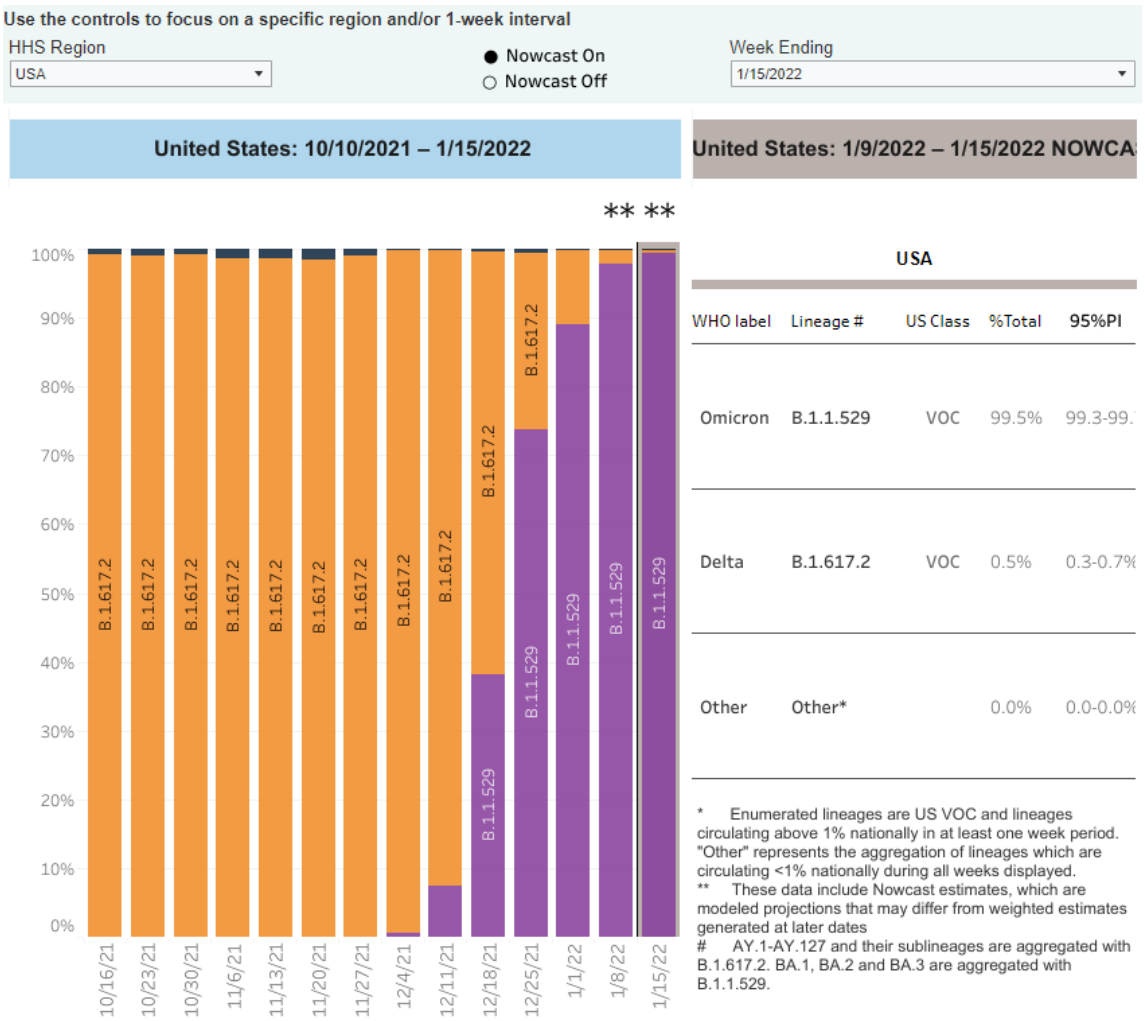

Figure 1: CDC Nowcast data ending the Week of January 15, 2022 source https://covid.cdc.gov/covid-data-tracker/#variant-proportions (accessed 01/22/2022)

Based on the above, the Division of Antivirals and Office of Infectious Diseases recommends adding the following new limitations on the authorized use of REGEN-COV for treatment of COVID-19 or as post-exposure prophylaxis for prevention of COVID-19, respectively:

Treatment

REGEN-COV is **not** authorized for treatment of mild to moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency.

Post-exposure prophylaxis

REGEN-COV is **not** authorized for post-exposure prophylaxis of COVID-19 in geographic regions where exposure is likely to have been to a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency.

Currently, there are no authorized or available point-of-care tests to accurately determine the SARS-CoV-2 variant that a patient is infected with; therefore, all therapy decisions are empiric and regional epidemiology is important to guide appropriate therapy choices. FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility (see, e.g., section 15 of authorized Fact Sheet for Health Care Providers), and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions. FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs. The Limitations of Authorized Use proposed above will ensure that, based on available information including variant susceptibility to REGEN-COV and regional variant frequency, any patient or individual receiving REGEN-COV consistent with the terms and conditions of the authorization will likely benefit from the therapy.

Additionally, on January 19, 2022, the NIH COVID-19 Treatment Guidelines Panel updated their recommendations to address the fact that Omicron is the dominant SARS-CoV-2 variant in the U.S. stating: "Because the anti-SARS-CoV-2 monoclonal antibodies (mAbs) bamlanivimab plus etesevimab and casirivimab plus imdevimab are predicted to have markedly reduced activities against this VOC, and because real-time testing to identify rare, non-Omicron variants is not routinely available, the Panel **recommends against** the use of these anti-SARS-CoV-2 mAbs **(AIII)**."[5]

The Agency recognizes that REGEN-COV may retain activity against other SARS-CoV-2 variants and that future circulating SARS-CoV-2 variants and the susceptibility patterns of our available countermeasures may shift. It's also important to underscore that the known and potential benefits of REGEN-COV when used to treat a patient with mild-to-moderate COVID-19 that is likely caused by a susceptible variant to this therapy, or when used as post-exposure prophylaxis of COVID-19 in an individual likely exposed to a variant susceptible to this therapy, consistent with the terms and conditions of the authorization, outweigh the known and potential risks of the product.

Moreover, the conditions to the authorization for REGEN-COV include requirements for monitoring and testing the authorized products against any global SARS-CoV-2 variant(s) of interest. Such requirements are essential to the Agency's continued understanding of REGEN-COV under this EUA.

[5] Source (accessed 1/21/2022) What's New | COVID-19 Treatment Guidelines (nih.gov)

Regulatory Conclusion and Associated Actions:

Based on the above, the Division of Antivirals and Office of Infectious Diseases believe that revision to the EUA for REGEN-COV as described above is appropriate to protect the public health or safety.

Consistent with the above, and concurrent with the revision to this EUA, FDA will also communicate publicly on the FDA website that REGEN-COV is not authorized for use in any U.S. region at this time.

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/

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