Emergency Use Authorization (EUA) for bamlanivimab 700 mg and etesevimab 1,400 IV

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)	94
Date of Memorandum	December 22, 2021
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Eli Lilly and Company: Christine Phillips, PhD, RAC Advisor, Global Regulatory Affairs - NA Mobile: (b) (6) Email: phillips_christine_ann@lilly.com
Manufacturer	Eli Lilly and Company
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Proprietary Name	n/a
Established Name/Other names used during development	bamlanivimab (LY3819253, LY-CoV555) and etesevimab (LY3832479, LY-CoV016)
Dosage Forms/Strengths	Bamlanivimab 700 mg and etesevimab 1400 mg IV
Therapeutic Class	SARS-CoV-2 spike protein directed human IgG1κ monoclonal antibody (mAb)
Intended Use or Need for EUA	Treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adult and pediatric patients, including neonates, 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 adults and pediatric individuals, including neonates, 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)	Adults and pediatric patients

Rationale and Revisions to EUA Fact Sheets

Limitations of Authorized Use and Antiviral Resistance Information in the Box and Section 15

The EUA for bamlanivimab and etesevimab was initially authorized on February 9, 2021. On August 27, 2021, FDA revised the EUA to include a Limitation on Authorized Use that provided that "bamlanivimab and etesevimab are not authorized for use in states, territories, and U.S. jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%." This revision was based on data showing that: (1) certain SARS-CoV-2 viral variants (P.1 and B.1.351) that were circulating at the time were resistant to bamlanivimab and etesevimab; and (2) other authorized monoclonal antibody therapies were (a) expected to be fully active against these and other circulating variants; and (b) available for use and distribution. As part of the August 27, 2021 revision, the Fact Sheet for Health Care Providers was also revised to inform health care providers about these other therapeutic options:

> There are other authorized monoclonal antibody treatments available and healthcare providers should choose an authorized therapeutic option with activity against circulating variants in their state. Variant frequency data for states and jurisdictions can be accessed on the following CDC website: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html

Circumstances have changed significantly since August 2021, and FDA has concluded that the Limitation on Authorized Use related to the combined frequency of variants above 5% that are resistant to bamlanivimab and etesevimab is no longer appropriate. The Omicron variant is currently spreading throughout the world. The first confirmed U.S. case of Omicron was identified on December 1, 2021. At this time, there remains significant uncertainty as to the specific prevalence of the Omicron variant in any particular state, territory, and U.S. jurisdiction. On December 20, 2021, CDC posted surveillance data stating that Omicron accounted for 0.7% (95%PI 0.4-1.1%) of the SARS-CoV-2 sequences for the week ending December 4, 2021. CDC's Nowcast uses model predictions to estimate the proportions of circulating variants to enable timely public health action. On December 20, 2021, the Nowcast model predicted that the frequency of the Omicron variant was 73.2%, with a wide prediction interval (95% PI 34.0-

94.9%). While this is a national estimate, there is also variability across the HHS regions of the U.S. with wide prediction intervals (e.g., HHS Region 7: 12/18/21, Omicron (B.1.1.529) 30.6% total (95% PI 1.6-85.1%), HHS Region 8: 12/18/21, Omicron (B.1.1.529) 62.7% total (95% PI 14.9-95.6%).[1] FDA anticipates that additional data regarding the prevalence of the Omicron variant in the various regions of the United States, and in territories and U.S. jurisdictions will be available in the coming weeks.

Based on the available data, it appears that some of the authorized monoclonal antibody therapies, including bamlanivimab and etesevimab, are unlikely to have activity against the Omicron variant (see Table 5 below taken from the Fact Sheet for Health Care Providers). Pseudotyped VLPs expressing the spike protein from the B.1.1.529/BA.1 show reduced susceptibility to bamlanivimab alone, etesevimab alone, and bamlanivimab and etesevimab together; rendering the drugs unlikely to have activity against the Omicron variant. However, bamlanivimab and etesevimab has been shown to retain activity against the Delta variant, which is continuing to circulate with high frequency, even in regions where the frequency of the Omicron variant may be above 5%. Additionally, certain authorized therapies that are expected to retain activity against the Omicron variant are expected to be limited in supply or in shortage, at least in the near term. Thus, at this time, it is no longer reasonable to presume that in geographic regions where the combined frequency of variants of concern is above 5% (which may soon be all geographic regions in the U.S.), health care providers will have access to other treatment options with a higher level of activity against circulating variants. Based on these factors, FDA believes that the Limitation on Authorized Use related to the combined frequency of variants above 5% that are resistant to bamlanivimab and etesevimab is no longer appropriate. In addition, FDA also believes that the EUA standard is met, including that the known and potential benefits of the product continue to outweigh the known and potential risks of the product, as reauthorized without this Limitation on Authorized Use. This is 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 bamlanivimab and etesevimab available for use given its activity against the Delta variant. Additionally, as stated in the Fact Sheet for Health Care Providers, bamlanivimab and etesevimab have generally been well tolerated, with the most significant safety concerns being hypersensitivity, including anaphylaxis and infusion-related reactions, but these events occurred at low rates (≤1%) in clinical trials. Because health care providers need to make empiric treatment decisions without knowing which circulating variant their patient may have, it is reasonable to use bamlanivimab and etesevimab given this safety profile, especially in areas with known Delta circulation. Moreover, it is still the case that there is no adequate, approved, and available alternative to the emergency use of bamlanivimab and etesevimab. Remdesivir (Veklury®) is the only drug that is approved by FDA to treat COVID-19 at this time, but remdesivir's approved indication is limited to the treatment of COVID- 19 in adults and pediatric patients (12 years of age and weighing at least 40 kg) requiring hospitalization.

Thus, the Limitation of Authorized Use has been removed from the Letter of Authorization and from the Fact Sheet for Health Care Providers.

The boxed portion of the fact sheet containing information related to SARS-CoV-2 Viral Variants has been modified and now directs health care providers to take variant frequency data into

[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.

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 U.S. 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:

- Pseudotyped VLPs expressing the spike protein from the B.1.1.529/BA.1 lineage (Omicron; South Africa origin), show reduced susceptibility to bamlanivimab alone (>1,465-fold), etesevimab alone (>616-fold), and bamlanivimab and etesevimab together (>2,938-fold).

- Due to the large reduction of pseudotyped VLP neutralization activity of both bamlanivimab and etesevimab against the substitutions in B.1.351 (Beta; South Africa origin), P.1 (Gamma; Brazil origin), AY.1/AY.2 (Delta [+K417N]; India origin), B.1.621 (Mu; Colombia origin), and B.1.1.529/BA.1 (Omicron; South Africa origin), it is unlikely that bamlanivimab and etesevimab together will be active against these variants.

The information below in red has been added to Table 5:

Table 5: Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Bamlanivimab and Etesevimab Together (1:2 Molar Ratio)

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested[a]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	no change[b]
B.1.351	South Africa	Beta	K417N + E484K + N501Y	431[c]
P.1	Brazil	Gamma	K417T + E484K + N501Y	252[c]
B.1.617.2/AY.3	India	Delta	L452R + T478K	no change[b]
AY.1/AY.2 (B.1.617.2 sublineages)	India	Delta [+K417N]	L452R + T478K + K417N	1,235[c]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	9[d]
B.1.526[e]	USA (New York)	Iota	E484K	30
B.1.617.1	India	Kappa	L452R + E484Q	6[d]
C.37	Peru	Lambda	L452Q + F490S	no change[b]
B.1.621	Colombia	Mu	R346K + E484K + N501Y	116[c]
B.1.1.529/BA.1	**South Africa**	**Omicron**	**G339D + S371L + S373P + S375F + K417N + N440K + G446S + S477N + T478K + E484A + Q493R + G493S + Q498R + N501Y + Y505H**	**>2,938[c]**

[a] Key substitutions occurring in the receptor binding domain of spike protein are listed. Pseudoviruses containing the full-length spike protein reflective of the consensus sequence for each of the variant lineages were tested.
[b] No change: <5-fold reduction in susceptibility.
[c] Bamlanivimab and etesevimab together are unlikely to be active against variants from this lineage.
[d] Etesevimab retains activity against this variant.
[e] Isolates of the B.1.526 lineage harbor several sp ke protein amino acid substitutions, and not all isolates contain the E484K substitution (as of February 2021).

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:

For the reasons described above, changes to the Letter of Authorization and Fact Sheet for Health Care Providers have been made that remove the restriction of only using bamlanivimab and etesevimab in states, territories, and U.S. jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%. 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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