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	August 27, 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)
Integrated Review Completion Date	February 9, 2021
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	mild to moderate COVID-19
Intended Population(s)	treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults 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

I. Issue Summary

This memorandum provides a brief summary of the changes to the Fact Sheet for Heath Care Providers and the Fact Sheet for Patients, Parents, and Caregivers for EUA 94 for bamlanivimab and etesevimab. The following are the most recent major changes made to the Fact Sheet for Health Care Providers authorized on August 27, 2021:

RECENT MAJOR CHANGES SINCE MAY 2021

- Authorized Use (Box and Section 1) – expanded the definition of progression of severe COVID-19 to include death.
- Limitations of Authorized Use (Box and Section 1) – change to authorized use related to the combined frequency of SARS-CoV-2 variants that are resistant to bamlanivimab and etesevimab.
- Antiviral Resistance (Box and Section 15) – addition of information on susceptibility of SARS-CoV-2 variants to bamlanivimab and etesevimab (Table 3 and Table 4) and updates based on latest viral surveillance report and additional sequencing data from Phase 3 study PYAB
- Warnings: Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions (Section 5.1) – addition of vasovagal reactions
- Warnings: Clinical Worsening After Bamlanivimab and Etesevimab Administration (Section 5.2) – updated to include administration with both antibodies

II. Rationale and Revisions to EUA Fact Sheets

Authorized Use (Box and Section 1)

Bamlanivimab and etesevimab were authorized for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults 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 and/or hospitalization on February 9, 2021. Additional Phase 3 data using the authorized dose of bamlanivimab 700 mg and etesevimab 1,400 mg were submitted to the Division of Antivirals in March 2021 demonstrating a mortality benefit similar to what was seen with bamlanivimab 2,800 mg and etesevimab 2,800 mg. In addition, Phase 3 data from other monoclonal antibodies in the same therapeutic class have also demonstrated a mortality benefit for those who are high risk for progression to severe disease compared to placebo. As such, the authorized use statement has been modified for agents in this therapeutic class to include death in the definition of severe COVID-19 given the demonstrated mortality benefit. The modified portions of the authorized use statement are highlighted in bold:

> The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved products bamlanivimab and etesevimab administered together for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults 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**.

Limitations of Authorized Use (Box and Section 1)

Since the initial authorization of bamlanivimab and etesevimab administered together for emergency use, there has been several SARS-CoV-2 viral variants that are resistant to bamlanivimab and etesevimab circulating throughout the United States. Given the emergence of viral variants of SARS-CoV-2, the Division requested that Lilly conduct cell culture neutralization studies to assess the activity of bamlanivimab and etesevimab against these variants, and/or amino acid substitutions found in these variants. The Sponsor provided pseudotyped virus-like particle (VLP) data for P.1/Gamma and B.1.351/Beta using spike variants reflective of the consensus sequences for each lineage. A large reduction in susceptibility was appreciated for B.1.351 and no activity was observed at the highest concentration tested for the P.1 variant. More modest changes in susceptibility were also appreciated for other variants of concern. Section 15 of the Fact Sheet for Health Care Providers was updated in March 2021 and May 2021 with the direction to health care providers to review these data related to 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 in their region to guide treatment decisions. The details of the EUA 94 Fact Sheet updates on the viral variants are provided in the revision memos dated March 17, 2021 and May 14, 2021.

Authorized labeling for bamlanivimab and etesevimab administered together advises healthcare providers to initiate treatment as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of onset of symptoms. Testing technologies are not available for healthcare providers to obtain information prior to initiating treatment to ascertain whether a patient who has tested positive for SARS-CoV-2 is infected with a particular viral variant that is resistant to bamlanivimab and etesevimab. As such, there is a significant risk of treatment failure should bamlanivimab and etesevimab be administered to a patient who is infected with a resistant SARS-CoV-2 variant. FDA and others have been monitoring the frequency of resistant variants in the US in order to minimize this risk.

In May 2021, given the likelihood that bamlanivimab and etesevimab were not active against P.1 and B.1.351, and because of the sustained increase in circulation of these variants, the U.S. Government, in coordination with Lilly, paused distribution of bamlanivimab and etesevimab together and etesevimab alone (to pair with existing supply of bamlanivimab at a facility for use under EUA 094) on a state-by-state basis whenever the combined frequency of P.1 and B.1.351 was determined to be greater than 10%. In addition, FDA recommended that health care providers in these states use alternative authorized monoclonal antibody therapies and not use bamlanivimab and etesevimab administered together until further notice. On June 25, 2021, the pause and recommendation to use alternative therapies were extended to all states, given that 11.6% of all sequenced isolates in the United States at that time were members of P.1. and B.1.351 lineages.

Since the pause in distribution, Eli Lilly has submitted, at the request of the Division of Antivirals, additional pseudotyped VLP data demonstrating that bamlanivimab and etesevimab have markedly reduced susceptibility to B.1.617.2 sublineages AY.1/AY.2 (commonly known as “Delta plus”; India origin) as well as B.1.621 (no designation; Colombia origin). However, pseudotyped VLP data was also submitted for B.1.617.2 (Delta; India origin) and the sublineage AY.3 demonstrating no change in susceptibility to bamlanivimab and etesevimab.

Since June 2021, there has been a sustained increase in the circulation of the B.1.617.2/Delta variant. Now in August 2021, the B.1.617.2/Delta variant is dominant in the U.S., with a subsequent decrease in the frequency of identified variants that are expected to be resistant to bamlanivimab and etesevimab. Based on these considerations and after continued internal discussions, it has been determined that the Limitations of Authorized Use should be modified to remove authorization for use in any state, territory, and US jurisdiction where combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%. While a 10% threshold had been used to guide decisions related to pauses in distribution, it is now believed that a 5% limit is more appropriate for the Limitation of Authorized Use in order to minimize treatment failure, given that treatment is empiric; as such it must be initiated without patient level sequencing information as there are no available point-of-care tests available to identify the circulating variants. This 5% threshold is also considered appropriate because other authorized monoclonal antibodies, that are expected to be fully active against all the circulating variants, are available for use and distribution.

In order to minimize the burden to health care providers, FDA will provide a listing of states, territories and US jurisdictions in which bamlanivimab and etesevimab currently are and are not authorized (https://www.fda.gov/media/151719/download). In collaboration with ASPR and CDC, it has been determined that bamlanivimab and etesevimab will be authorized when under the following conditions:

1. An HHS Region has a combined proportion of variants resistant to bamlanivimab and etesevimab that is less than or equal to 5% over a 4 week period.
2. No state within the HHS Region has a combined proportion of variants resistant to bamlanivimab and etesevimab greater than 5%.
3. The two most recent weeks of data from Nowcast predicts the combined prevalence of variants resistant to bamlanivimab and etesevimab will remain below 5%.

At the present time, based on publicly available information (https://covid.cdc.gov/covid-data-tracker/#variant-proportions), the combined prevalence of AY.1, AY.2, P.1, B.1.351, B.1.621, and B.1.621.1 is being used for consideration of criteria 1 and 3; the combined prevalence of AY.1, AY.2, P.1, and B.1.351 is being used for criterion 2. Of note, these methodologies may change as more data become publicly available.

The Limitations of Authorized Use has now been modified to include the following statements:

- Bamlanivimab and etesevimab are not authorized for use in states, territories, and US jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%.[1]
    - A list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized is available on the following FDA website: https://www.fda.gov/media/151719/download

The footnote provides the following information:

[1]FDA will make this determination considering current variant frequency data (available at: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html), trends in variant frequency over time, the precision of the estimates and information regarding emerging variants of concern. FDA will update the list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized as new data and information becomes available. Healthcare providers should refer to the FDA website regularly for updates.

Additional information for clinical consideration is also included in the Box within the Fact Sheet for Health Care Providers:

- Review travel and contact history within 2 weeks prior to infection. Persons who have traveled to, resided in, or had close contact with an infected individual from an area where the frequency of resistant variants to bamlanivimab and etesevimab exceeds 5% should not receive bamlanivimab and etesevimab. Other monoclonal antibody therapy options should be considered.
- There are other authorized monoclonal antibody treatments available and healthcare providers should choose an authorized therapeutic option with activity against the circulating variants in their state, territory, or US jurisdiction.
- Healthcare providers should also refer to Section 15 of this Fact Sheet for further details regarding specific variants and resistance.

Antiviral Resistance (Section 15)

It is noted in Section 15 of the Fact Sheet for Health Care Providers that there is a potential risk of treatment failure due to the development of viral variants that are resistant to bamlanivimab and/or etesevimab. In this update of the Fact Sheet for Health Care Providers, additional guidance is given as follows:

> 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.

A footnote provides a link to the FDA website that lists states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized.

FDA has requested that Lilly provide consistent updates regarding activity of bamlanivimab and etesevimab against SARS-CoV-2 variants circulating in the United States. Additional data, as well as inclusion of new WHO nomenclature, are now included in Section 15 Antiviral Resistance. Note that information included on the B.1.621 variant is included in the language above Table 3 and not in Table 3. These data are from an independent lab and were submitted under EUA 94. Updates to Table 3 may be made once confirmation of the data are available from Eli Lilly and Company are complete. Changes to this section are bolded below:

> Resistant variants were identified using directed evolution of the spike protein and serial passage in cell culture of SARS-CoV-2 in the presence of bamlanivimab or etesevimab individually. Resistant variants were not identified when bamlanivimab and etesevimab were tested together using the same methodology. Viral variants identified in these studies that had reduced susceptibility to bamlanivimab included spike protein amino acid substitutions E484D/K/Q, F490S, Q493R, and S494P, and variants that had reduced susceptibility to etesevimab included substitutions K417N, D420N, and N460K/S/T/Y. **Neutralization assays using SARS-CoV-2 and vesicular stomatitis virus (VSV) virus-like particles (VLP) pseudotyped with variant SARS-CoV-2 spike protein confirmed reductions in susceptibility to the selecting antibody**. Retention of susceptibility to the other antibody alone was observed, with the exception of the **E484D and** Q493R substitution. All variants maintained susceptibility to bamlanivimab and etesevimab together, with the exception of those with **E484D**, E484K, E484Q, and Q493R substitutions, which had reduced susceptibility of **145-fold, 24-fold, 17-fold**, and >100-fold, respectively in a pseudotyped VLP assay.
>
> Evaluation of susceptibility of variants identified through global surveillance in subjects treated with bamlanivimab and etesevimab is ongoing. Pseudotyped VLP evaluation of amino acid substitutions identified in global surveillance showed that the V483A substitution reduced

susceptibility to bamlanivimab 48-fold, but activity was maintained with etesevimab, and with bamlanivimab and etesevimab together. N501Y and N501T substitutions reduced susceptibility to etesevimab approximately 5-fold and 20-fold, respectively. Activity against variants with N501Y or N501T substitutions was maintained with bamlanivimab alone, and with bamlanivimab and etesevimab together.

Bamlanivimab and etesevimab together retained activity against a SARS-CoV-2 B.1.1.7 lineage (**Alpha**; UK origin) virus and related pseudotyped VLPs expressing **the spike protein** found in the B.1.1.7 variant (**Tables 3 and 4**). **SARS-CoV-2** B.1.351 lineage (**Beta**; South Africa origin) virus and **related pseudotyped VLPs expressing spike proteins from B.1.351 lineage or substitutions** K417N + E484K + N501Y found in this lineage had reduced susceptibility to bamlanivimab and etesevimab together of >**324, 431-fold** or >45-fold, respectively. Pseudotyped VLPs expressing spike protein from the P.1 lineage (**Gamma**; Brazil origin) or K417T + E484K + N501Y found in the P.1 lineage had reduced susceptibility to bamlanivimab and etesevimab together of **252-fold or >511-fold, respectively.**

Bamlanivimab and etesevimab together and etesevimab alone retained activity against SARS-CoV-2 B.1.617.2 lineage (Delta; India origin) virus and related pseudotyped VLPs, but bamlanivimab alone had reduced activity (>1,136 and >1,868-fold, respectively). Bamlanivimab and etesevimab are expected to retain activity against B.1.617.2 sublineage AY.3 (India origin). B.1.617.2 sublineages AY.1/AY.2 (commonly known as "Delta plus"; India origin) have an additional K417N substitution; pseudotyped VLPs expressing AY.1/AY.2 related spike sequence had a reduced susceptibility to bamlanivimab and etesevimab together of 1,235-fold. SARS-CoV-2 recombinant virus containing the L452R substitution present in the B.1.427/B.1.429 lineages (Epsilon; **USA [California] origin) and pseudotyped VLPs expressing the full-length spike protein or the L452R substitution found in this lineage showed reduced susceptibility to bamlanivimab and etesevimab together of 11-fold, 9-fold or 5-fold, respectively**. **Pseudotyped VLPs expressing spike protein from the B.1.617.1 lineage (Kappa; India origin) showed reduced susceptibility to bamlanivimab and etesevimab together of 6-fold; for this variant, susceptibility to etesevimab alone was maintained, but not to bamlanivimab alone (>1,030-fold reduction). Pseudotyped VLPs expressing spike protein from the B.1.621 lineage (no designation;**

Colombia origin) show reduced susceptibility to bamlanivimab and etesevimab together of 133-fold based on an independent evaluation.

Table 3: 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][d]**	**L452R + T478K + K417N**	**1,235[c]**
B.1.427/B.1.429	**USA (California)**	**Epsilon**	L452R	9[e]
B.1.526[f]	**USA (New York)**	**Iota**	E484K	30
B.1.617.1	**India**	**Kappa**	**L452R + E484Q**	**6[e]**

[a] For variants with more than one substitution of concern, only the substitution(s) with the greatest impact on activity is(are) listed. For B.1.351, P.1, B.1.427/B.1.429, **B.1.526, B.1.617.1, B.1.617.2, and AY.1/AY.2** spike variants reflective of the consensus sequence for the lineage 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] **Commonly known as "Delta plus."**
[e] Etesevimab retains activity against this variant.
[f] 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).

Table 4: Authentic[a] SARS-CoV-2 Neutralization Data for Bamlanivimab and Etesevimab Together (1:2 Molar Ratio)

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested[b]	Fold Reduction in Susceptibility
B.1.1.7	**UK**	**Alpha**	N501Y	no change[c]
B.1.351	**South Africa**	**Beta**	**K417N + E484K + N501Y**	**>325**
B.1.617.2/AY.3	**India**	**Delta**	**L452R, T478K**	**no change[c]**
B.1.427/B.1.429	**USA (California)**	**Epsilon**	**L452R**	**11**
B.1.526[d]	**USA (New York)**	**Iota**	E484K	**11**

[a] The B.1.1.7 variant was assessed using cell culture-expanded virus isolates **and tested using an immunofluorescence based microneutralization assay and by plaque reduction assay**; **B.1.351 and B.1.617.2 variants were assessed using cell culture-expanded virus isolates and tested using a plaque reduction assay**; the B.1.526/E484K **and B.1.427/B.1.429/L452R**

substitutions were assessed using recombinant SARS-CoV-2 (USA/WA/1/2020 isolate **with E484K or L452R) and tested using a plaque reduction assay.**

[b] For variants with more than one substitution of concern, only the one(s) with the greatest impact on activity is(are) listed.

[c] No change: <5-fold reduction in susceptibility.

[d] 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). This assay was conducted using recombinant SARS-CoV-2 with the E484K substitution only.

Due to the lack 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 plus"; India origin)**, **and B.1.621 (no designation; Colombia origin),** it is unlikely that bamlanivimab and etesevimab together will be active against these variants.

It is unclear how small reductions in susceptibility to bamlanivimab and etesevimab seen in authentic or recombinant SARS-CoV-2 or pseudotyped VLP assays correlate with clinical outcomes.

In authentic SARS-CoV-2 assays, bamlanivimab and etesevimab together retained activity against variants of B.1.1.7 (Alpha) and B.1.617.2/AY.3 (Delta) lineages (Table 4). SARS-CoV-2 (USA/WA/1/2020 isolate) engineered to express the E484K substitution present in the B.1.526 lineage (Iota; USA [New York] origin) or the L452R substitution present in the B.1.427/B.1.429 lineage (Epsilon; USA [California] origin) showed reduced susceptibility to bamlanivimab and etesevimab together of 11-fold. Susceptibility to etesevimab alone was maintained for both isolates, but not to bamlanivimab alone (>833-fold and >1,460-fold reduction for E484K and L452R viruses, respectively). Available nonclinical and clinical PK data indicate that etesevimab at the authorized dose may retain activity against the B.1.526 variant clinically, although only very limited data are currently available from patients infected with this variant in clinical trials. Preliminary clinical evidence indicates that the administration of bamlanivimab and etesevimab together result in similar viral load reductions in participants infected with the L452R variant (**Epsilon; USA** [California] origin) as observed in those who were infected with bamlanivimab-sensitive strains. Of the 134 participants infected with the L452R variant at baseline in the Phase 3 portion of BLAZE-1, 3 of the 50 individuals treated with placebo (6%) and 1 of the 84 participants treated with bamlanivimab 700 mg and etesevimab 1,400 mg (1%) were hospitalized (p=0.15).

Genotypic and phenotypic testing are ongoing to monitor for potential bamlanivimab- and etesevimab-resistance associated spike variations in clinical trials. Analysis of baseline samples show that **8.4% (188/2246)** of clinical trial patients were infected with viral variants containing single amino acid substitutions at positions associated with reduced susceptibility to either bamlanivimab or etesevimab as predicted by pseudotyped VLP o**r authentic SARS-CoV-2 neutralization assays**. **No patients were infected with a variant** that was predicted to have reduced susceptibility to both bamlanivimab and etesevimab **by these assessments.**

Patient samples were also analyzed for treatment-emergent viral variants, defined as variants with single amino acid substitutions at positions that had reduced susceptibility to either bamlanivimab or etesevimab present at an allele fraction of ≥15%.

- In the Phase 3 portion of BLAZE-1, treatment-emergent variants were observed in **9.0% (42/467)** of patients treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together, in **5.3% (21/394)** of patients treated with bamlanivimab 700 mg and etesevimab 1,400 mg together, and in **4.0% (27/674)** of patients treated with placebo. **The majority of these were only detected at one time point in the sequential series with 0.9% (4/467), 1.0% (4/394), and 0.3% (2/674) of patients having multiple instances of detection in the bamlanivimab 2,800 mg and etesevimab 2,800 mg together, bamlanivimab 700 mg and etesevimab 1,400 mg together, and placebo groups, respectively.**
- In patients treated with bamlanivimab and etesevimab together, substitutions detected in one or more patients included ones with reduced susceptibility (≥5-fold) to

bamlanivimab only: L452R, E484K, G485V, and S494P; and ones with reduced susceptibility to etesevimab only: D405G/Y, K417N, D420N**/Y**, N460**I/**T, **A475V, Y489H,** and N501I/ Y. While these variants had reduced susceptibility to either bamlanivimab OR etesevimab compared to wild-type in a pseudotyped VSV VLP or authentic virus assay they still retained susceptibility to the other antibody in the combination.

- There were also observations of variants with reduced susceptibility (≥5-fold) to both bamlanivimab and etesevimab **or to bamlanivimab + etesevimab tested together**: **E484D (n=1; no neutralization by either antibody),** F490L **(n=3; 13-fold reduction to bamlanivimab + etesevimab together**), **and Q493K/R (n=9; no neutralization by either antibody) out of a total of 861 patients treated with bamlanivimab and etesevimab together.**
- **In a subgroup of participants infected with virus harboring L452R substitution found in the B.1.427/B.1.429 (Epsilon) lineage, a S459P treatment-emergent substitution was identified in one subject. Concurrent L452R+S459P substitutions conferred a 1,656-fold reduction in susceptibility to bamlanivimab + etesevimab together (1:2 molar ratio).**
- Additional treatment-emergent substitutions in patients treated with bamlanivimab and etesevimab together, with no phenotypic data, include D405del, **D420G**, **K444N/R, N460H, A475S/T, C480R,** G485D, S494L, **and P499L.** The impact of these substitutions **on susceptibility** is not currently known.

It is possible that bamlanivimab and etesevimab resistance-associated variants could have cross-resistance to other mAbs targeting the receptor binding domain of SARS-CoV-2. The clinical impact is not known.

Warnings: Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions (Section 5.1)

Safety of bamlanivimab and etesevimab under EUA continues to be monitored by the Division of Pharmacovigilance, in coordination with the Division of Antivirals. Following the review of safety reports of bamlanivimab and etesevimab under EUA, modifications have been made to Section 5.1 to communicate that infusion related reactions could occur up to 24 hours after infusion and that vasovagal reactions have been reported. The updated language is highlighted in bold:

Infusion-related reactions, **occurring during the infusion and up to 24 hours after the infusion**, have been observed with administration of bamlanivimab and etesevimab together. These reactions may be severe or life threatening.

Signs and symptoms of infusion related reactions may include:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, **vasovagal reactions (e.g., pre-syncope, syncope)**, dizziness and diaphoresis.

Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion-related reaction occurs.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of bamlanivimab with and without etesevimab under Emergency Use Authorization.

“Feeling faint” is now also included as a possible side effect of bamlanivimab and etesevimab in the Fact Sheet for Patients, Parents, and Caregivers.

Warnings: Clinical Worsening After Bamlanivimab and Etesevimab Administration (Section 5.2)

Based on ongoing pharmacovigilance and review of safety reporting, this section was updated to make the warning inclusive of bamlanivimab and etesevimab administered together, rather than bamlanivimab alone. The updated language is highlighted in bold below:

> Clinical worsening of COVID-19 after administration of bamlanivimab **and etesevimab together** has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to bamlanivimab **and etesevimab** use or were due to progression of COVID-19.

A similar edit was added to the Fact Sheet for Patients, Parents, and Caregivers to convey that a risk of worsening of symptoms after treatment with both bamlanivimab and etesevimab may occur.

Regulatory Conclusion:

Given the totality of evidence, it has been determined that the Limitations of Authorized Use should be modified to remove authorization for use of bamlanivimab and etesevimab in any state, territory, and US jurisdiction where the combined frequency SARS-CoV-2 resistant variants exceeds 5%. This change to the Limitation of Authorized Use has been made in order to minimize the risk of treatment failure and to provide health care providers with the most current information as to when it is appropriate to the use bamlanivimab and etesevimab together for the treatment of COVID-19. Additionally, updates to communicate the most recent resistance data and safety information were added to the Fact Sheet for Health Care Providers as well as the Fact Sheet for Patients, Parents, and Caregivers. Collectively, the revisions to the Fact Sheets detailed above do not alter the analysis of benefits and risks that underlies the initial authorization of EUA 94.

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/

NATALIE M PICA
08/27/2021 11:28:48 AM

WENDY W CARTER
08/27/2021 11:36:18 AM

DEBRA B BIRNKRANT
08/27/2021 11:36:51 AM

JOHN J FARLEY
08/27/2021 11:39:30 AM