Frequently Asked Questions on the Emergency Use Authorization for Bamlanivimab and Etesevimab

Q. What is an Emergency Use Authorization (EUA)?
A: Under section 564 of the Federal Food, Drug & Cosmetic Act, after a declaration by the HHS Secretary based on one of four types of determinations, FDA may authorize an unapproved product or unapproved uses of an approved product for emergency use. In issuing an EUA, FDA must determine, among other things, that based on the totality of scientific evidence available, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; that the known and potential benefits, when used to treat, diagnose or prevent such disease or condition, outweigh the known and potential risks for the product; and that there are no adequate, approved, and available alternatives. Emergency use authorization is NOT the same as FDA approval or licensure.

Q. What does this EUA authorize?
A. The EUA authorizes Eli Lilly and Company's (Lilly's) bamlanivimab and etesevimab, administered together, for emergency use for both treatment and as post-exposure prophylaxis (prevention) of COVID-19.

Treatment:

Treatment of mild-to-moderate 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.

Post-Exposure Prophylaxis (Prevention):

For use as post-exposure prophylaxis of COVID-19 in individuals who are at high risk of 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**
    - 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
    - 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 and prisons)

In general, people are considered fully vaccinated two weeks after their second dose in a two dose series (the Pfizer or Moderna vaccines) OR two weeks after a single-dose vaccine (the Janssen vaccine).

The CDC defines close contact as someone who has been within six feet of an infected person (laboratory-confirmed or a clinically compatible illness) for a cumulative total of 15 minutes or more over a 24-hour period.

Q. What are the limitations of authorized use?
A. Bamlanivimab and etesevimab, administered together, are **not authorized** for use in states, territories, and U.S. jurisdictions in which the most recently published combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%. Health care providers should review travel and contact history from two weeks prior to infection. People 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.

FDA posted the list of states, territories, and U.S. jurisdictions with their respective authorization status for bamlanivimab and etesevimab, administered together, as new data and information becomes available. FDA will make this determination considering current variant frequency data, trends in variant frequency over time, the precision of the estimates, and information regarding emerging variants of concern. Health care providers should refer to this FDA website regularly for updates.

Bamlanivimab and etesevimab are not authorized for use in patients:

- who are hospitalized due to COVID-19, OR
- who require oxygen therapy due to COVID-19, OR
- who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Post-exposure prophylaxis with bamlanivimab and etesevimab is not a substitute for vaccination against COVID-19. Bamlanivimab and etesevimab are not authorized for pre-exposure prophylaxis for prevention of COVID-19.

Q. How is high risk defined under the EUA?
A. The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example age ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)

- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of bamlanivimab and etesevimab under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: People with Certain Medical Conditions. Health care providers should consider the benefit-risk for an individual patient.

Q: Can adults weighing less than 40 kg receive bamlanivimab and etesevimab?
A: Yes. Bamlanivimab and etesevimab, administered together, are 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, including hospitalization or death. Adults can be treated regardless of their weight; pediatric patients must be at least 12 years of age and weigh at least 40 kg.

Q. Bamlanivimab and etesevimab administered together are authorized for the treatment of mild-to-moderate 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. What does direct SARS-CoV-2 viral testing mean?
A. Direct SARS-CoV-2 viral tests diagnose active COVID-19 infection. Direct SARS-CoV-2 viral tests include two types of diagnostic tests for COVID-19:

- Molecular tests, such as RT-PCR tests, that detect the virus's genetic material
- Antigen tests that detect specific proteins from the virus

Antibody tests should not be used to diagnose COVID-19 and are not direct SARS-CoV-2 viral tests. Antibody tests look for antibodies made by the immune system in response to the SARS-CoV-2 virus.

Q: How are bamlanivimab and etesevimab, administered together, affected by the SARS-CoV-2 viral variants in the United States?
A: Based on results from in vitro assays that are used to assess the susceptibility of viral variants to monoclonal antibody therapies, bamlanivimab and etesevimab, administered together, **are not** expected to retain activity against the SARS-CoV-2 P.1/Gamma variant (first identified in Brazil), the B.1.351/Beta variant (first identified in South Africa), the AY.1 and AY.2 variants/Delta[+K417N] (commonly known as "Delta plus," first identified in India) or the B.1.621 variant/Mu (first identified in Colombia). These assays use "pseudotyped virus-like particles" that help determine likely susceptibility of the live SARS-CoV-2 variant viruses.

Bamlanivimab and etesevimab, administered together, are **not authorized** for use in states, territories, and U.S. jurisdictions in which the most recently published combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%. Health care providers should review travel and contact history from two weeks prior to infection. People 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.

FDA has posted a list of states, territories, and U.S. jurisdictions with their respective authorization status for bamlanivimab and etesevimab, administered together, and will periodically update this list as new data and information becomes available. FDA will make its determinations on authorization status by considering current variant frequency data, trends in variant frequency over time, the precision of the estimates, and information regarding emerging variants of concern. Health care providers should refer to this FDA website regularly for updates. The prevalence of these variants is being monitored by FDA, CDC, and other stakeholders.

Health care providers should also review the Antiviral Resistance information in Section 15 of the authorized Fact Sheets for each monoclonal antibody therapy available under an EUA, including bamlanivimab and etesevimab, for details regarding specific variants and resistance.

Q. How can bamlanivimab and etesevimab be obtained for use under the EUA?
A. For questions on how to obtain bamlanivimab and etesevimab, or etesevimab alone to pair with an existing supply of bamlanivimab under current distribution procedures, please contact COVID19therapeutics@hhs.gov.

Q. Are bamlanivimab and etesevimab monoclonal antibodies? What is a monoclonal antibody?
A. Yes, bamlanivimab and etesevimab are monoclonal antibodies. Monoclonal antibodies are laboratory-produced molecules engineered to serve as substitute antibodies that can restore, enhance or mimic the immune system's attack on pathogens. Bamlanivimab and etesevimab are designed to block viral attachment and entry into human cells, thus neutralizing the virus.

Q. When should bamlanivimab and etesevimab be administered to a patient?
A. For treatment, bamlanivimab (700 mg) and etesevimab (1,400 mg) are administered together as a single intravenous infusion. It is recommended that bamlanivimab and etesevimab be administered as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset.

For post-exposure prophylaxis, 700 mg bamlanivimab and 1,400 mg etesevimab should be administered together as a single intravenous infusion as soon as possible following exposure to SARS-CoV-2.

More information about administration for treatment and post-exposure prophylaxis is available in the Fact Sheet for Health Care Providers.

Q: Does "within 10 days of symptom onset" mean that a patient should have shown symptoms to receive bamlanivimab and etesevimab administered together for its treatment use?

A. Yes. Symptom onset is the point at which a patient starts exhibiting symptoms. Patients should be treated as soon as possible after a positive viral test for SARS-CoV-2 **and** within ten days of COVID-19 symptom onset. If a patient has a positive viral test for SARS-CoV-2 but does not show symptoms, they do not meet the definition of mild-to-moderate disease.

Bamlanivimab and etesevimab are authorized for emergency use by FDA for the treatment of mild-to-moderate 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. Patients with mild-to-moderate COVID-19 are those

patients who are actively exhibiting certain symptoms of COVID-19 illness (such as, fever, cough, sore throat, headache, malaise, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell).

For more information on mild-to-moderate COVID-19, refer to the National Institutes of Health's website at: Clinical Spectrum | COVID-19 Treatment Guidelines (nih.gov).

Therefore, patients who are at high risk for progression to severe COVID-19, including hospitalization or death, with mild-to-moderate COVID-19 disease (i.e., symptoms consistent with mild-to-moderate illness at the time of treatment) and who are within 10 days of symptom onset are within the scope of the EUA.

Q. Where are infusions of bamlanivimab and etesevimab available?
A. The following websites contain information regarding access to monoclonal antibody treatments for COVID-19:

- HHS Protect Public Data Hub – Therapeutics Distribution
- National Infusion Center Association (NICA)

Bamlanivimab and etesevimab may only be administered together in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and have the ability to activate the emergency medical system (EMS), if necessary. Please speak with your doctor or contact your local or state public health department for more information.

Q. Are bamlanivimab and etesevimab approved by the FDA to treat COVID-19?
A. No. They are not currently FDA-approved to treat any diseases or conditions, including COVID-19. Bamlanivimab and etesevimab are investigational drugs.

Q. Does the EUA permit the use of bamlanivimab and etesevimab as authorized in patients hospitalized *for reasons other* than COVID-19?
A. Bamlanivimab and etesevimab, administered together, are authorized for emergency use for the treatment of mild-to-moderate 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 progressing to severe COVID-19 and/or hospitalization. If a patient is hospitalized *for reasons other* than COVID-19, such as for an elective orthopedic procedure for example, and the patient reports mild to moderate symptoms of COVID-19, confirmed with positive results of a direct SARS-CoV-2 viral test, then it may be appropriate to treat the patient with bamlanivimab and etesevimab, administered together, if the patient is also at high risk for progressing to severe COVID-19 and/or hospitalization and the terms and conditions of the authorization are met, as detailed in the Fact Sheet for Health Care Providers.

Q. Are there data showing treatment with bamlanivimab and etesevimab, administered together, might benefit patients with mild-to-moderate COVID-19? Or as post-exposure prophylaxis of COVID-19?
A. Yes. The strongest evidence supporting the issuance of this EUA for bamlanivimab and etesevimab, administered together, as treatment comes from the phase 3 portion of a randomized, double-blind, placebo-controlled clinical trial (BLAZE-1) in 769 non-hospitalized adults with mild-to-moderate COVID-19 symptoms who were at high risk for progression to severe COVID-19. Of these patients, 511 received a single infusion of bamlanivimab 700 mg and etesevimab 1,400 mg together and 258 received placebo.

The primary endpoint was COVID-19 related hospitalizations or death by any cause during 29 days of follow-up. Hospitalization or death occurred in 15 (6%) patients who received placebo compared to 4 (0.8%) patients treated with bamlanivimab 700 mg and etesevimab 1,400 mg administered together ($p<0.001$), an 87% reduction. All deaths (n = 4, 1.6%) occurred in the placebo group. Thus, all-cause mortality was significantly lower in the bamlanivimab 700 mg and etesevimab 1,400 mg group than the placebo group ($p=0.01$). In addition, patients that received bamlanivimab 700 mg and etesevimab 1,400 mg together had a faster time to symptom resolution in the clinical trial.

The primary data supporting the post-exposure prophylaxis of COVID-19 are from the Phase 3 trial BLAZE-2. BLAZE-2 Part 1 is a randomized, double-blind, placebo-controlled study evaluating bamlanivimab alone for prevention of COVID-19 in residents and staff of skilled nursing facilities following a confirmed reported case of SARS-CoV-2 infection at the facility. All participants in Part 1 were randomized and treated with a single infusion of bamlanivimab 4,200 mg or placebo. Results of baseline testing for SARS-CoV-2 were not known until after the therapy was administered. Those with a positive baseline SARS-CoV-2 RT-PCR test were included in the Treatment Population (N=132) and those with a negative test were included in the Prevention Population (N=966). The primary endpoint (cases of symptomatic COVID-19 by Day 57) was assessed after all participants in the Prevention Population reached 8 weeks of follow-up, and analysis were adjusted for facility, sex, and role within facility (resident/staff). The Treatment Population was analyzed separately and not included in the primary endpoint for this prevention trial.

In the Prevention Population, there were 114 cases of symptomatic COVID-19, with a lower frequency occurring in participants treated with bamlanivimab as compared to placebo (residents and staff; adjusted odds ratio 0.43; $p<0.001$) reducing the risk of being infected with COVID-19 by up to 57%. For the pre-specified subgroup of nursing home residents, there were 45 cases of symptomatic COVID-19, with a lower frequency in those treated with bamlanivimab versus placebo (adjusted odds ratio 0.20; $p<0.001$), reducing the risk of being infected with COVID-19 by up to 80%. For the post-hoc subgroup of patients who met the high-risk criteria (all residents and all high-risk staff), there were 75 cases of symptomatic COVID-19, with a lower frequency in those treated with bamlanivimab versus placebo (adjusted odds ratio 0.28; nominal $p<0.001$), reducing the risk of being infected with COVID-19 by up to 72%.

While BLAZE-2 only evaluated dosing with bamlanivimab alone, it is reasonable to expect that bamlanivimab and etesevimab administered together may be safe and effective for post-exposure prophylaxis based on:

- Bamlanivimab and etesevimab administered together showed a statistically significant reduction in progression of severe COVID-19, including hospitalization or death, in high-risk patients with mild-to-moderate COVID-19 (Phase 3 data from BLAZE-1 treatment trial).
- Nonclinical and clinical data support that bamlanivimab and etesevimab administered together will provide an advantage over bamlanivimab alone against certain SARS-CoV-2 viral variants.

Details on the clinical trial results can be found in Section 18 of the authorized Fact Sheet for Health Care Providers.

Q. Are there clinical trials underway evaluating bamlanivimab and etesevimab for COVID-19?
A. Yes. Clinical trials remain ongoing to study bamlanivimab and etesevimab for investigational uses.

Q. Are there side effects of bamlanivimab and etesevimab?
A. Approximately 1,400 non-hospitalized subjects have received bamlanivimab and etesevimab administered together in clinical trials at doses of bamlanivimab 700 mg and etesevimab 1,400 mg or higher. Bamlanivimab and etesevimab at the authorized doses of 700 mg and 1,400 mg have been administered together to approximately 800 subjects.

Serious hypersensitivity reactions, including anaphylaxis and fainting (vasovagal), have been observed with administration of bamlanivimab and etesevimab. In clinical trials, these reactions have been rare, but may be severe or life threatening.

Based on reporting of adverse events that occurred after administration of bamlanivimab alone under EUA, clinical worsening of COVID-19 after administration of bamlanivimab 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 use or were due to progression of COVID-19.

Nausea, dizziness, and pruritus were the most commonly reported adverse events after administration of bamlanivimab and etesevimab together.

Q. Are bamlanivimab and etesevimab co-packaged?
A. At this time, bamlanivimab is not co-packaged with etesevimab under this EUA. While these products are not co-packaged, etesevimab cannot be used alone and must be administered with bamlanivimab. Bamlanivimab cannot be used alone as this use is no longer authorized. Bamlanivimab and etesevimab must be administered together.

Q. Are there reporting requirements for health care facilities and providers as part of the EUA?
A. Yes. As part of the EUA, FDA requires health care providers who prescribe bamlanivimab and etesevimab together to report all medication errors and serious adverse events considered to be potentially related to bamlanivimab and etesevimab through FDA's MedWatch Adverse Event Reporting program. Providers can complete and submit the report online; or download and complete the form, then submit it via fax at 1-800-FDA-0178. This requirement is outlined in the EUA's health care provider Fact Sheet. FDA MedWatch forms should also be provided to Lilly.

Health care facilities and providers must report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services. Such information and data should be reported through HHS Protect, Teletracking, or National Health care Safety Network (NHSN).

Q. Do patient outcomes need to be reported under the EUA?
A. No, reporting of patient outcomes is not required under the EUA. However, reporting of all medication errors and serious adverse events considered to be potentially related to bamlanivimab and etesevimab, administered together, occurring during treatment is required.

Q. Does the EUA authorize bamlanivimab and etesevimab, administered together, to be used as pre-exposure prophylaxis for COVID-19?
A. No. Use of bamlanivimab and etesevimab, administered together, for the pre-exposure prophylaxis of COVID-19 is not authorized.

Q. Can health care providers share the patient/caregiver Fact Sheet electronically?
A. The letter of authorization for bamlanivimab and etesevimab, administered together, requires that Fact Sheets be made available to health care providers and to patients/caregivers "through appropriate means." Electronic delivery of the Fact Sheet is an appropriate means. For example, when the patient requests the Fact Sheet electronically, it can be delivered as a PDF prior to medication administration. Health care providers should confirm receipt of the Fact Sheet with the patient.

Q. Is there likely to be an increased risk of infusion-related reactions with shorter versus longer infusion times?
A. FDA does not anticipate an increased risk of infusion-related reactions with the shorter infusion times or use of different size saline bags for dilution authorized. The preparation and administration instructions, including the shorter durations of infusion with smaller volumes of diluent were based on data evaluated by FDA including product quality data and data from clinical trials.

Q. Can I receive a COVID-19 vaccine if I was treated with a monoclonal antibody for COVID-19?
A. Health care providers should refer to recommendations of the Advisory Committee on Immunization Practices regarding vaccination.