



February 11, 2021

Bamlanivimab and Etesevimab (Eli Lilly and Company) - EMERGENCY USE AUTHORIZATION -

Mechanism of action¹: Bamlanivimab and etesevimab are neutralizing IgG1 monoclonal antibodies that bind to distinct but overlapping epitopes within the receptor binding domain of the spike protein of SARS-CoV2.

Current Status^{1,2}: Bamlanivimab and etesevimab are not FDA approved, they are an investigational drug combination and are not currently approved for any indication. On February 9, 2021, the FDA issued an Emergency Use Authorization (EUA) to permit emergency use of the unapproved products bamlanivimab and etesevimab administered together 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.

High risk is defined as patients who meet at least one of the following criteria:

- Have a body mass index (BMI) ≥ 35
- Have chronic kidney disease, diabetes, or an immunosuppressive disease, or are receiving immunosuppressive treatment
- Are ≥ 65 years of age
- Are ≥ 55 years of age AND have:
 - cardiovascular disease OR hypertension OR COPD / other chronic respiratory disease.
- Are 12 – 17 years of age AND have:
 - BMI ≥ 85 th percentile for their age and gender based on [CDC growth charts](#), OR
 - sickle cell disease OR congenital or acquired heart disease, OR
 - neurodevelopmental disorders, for example, cerebral palsy, OR
 - a medical-related technological dependence (e.g., tracheostomy, gastrostomy), OR
 - asthma, reactive airway or other chronic respiratory disease requiring daily medication for control

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.**

Therefore, 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.

Availability: Distribution of bamlanivimab and etesevimab will be controlled by the U.S. Government for use consistent with the terms and conditions of the EUA. More information will be made available [here](#).

Dosing and Administration²: Bamlanivimab and etesevimab **must be administered together after dilution by IV infusion only** and may only be administered in settings in which providers have immediate access to medications to treat a severe infusion reaction and can activate the emergency medical system as necessary.

- The dosage is 700 mg bamlanivimab and 1400 mg of etesevimab administered together as a single IV infusion as soon as possible after positive test for SARS-CoV-2 and within ten days of symptom onset.
- Bamlanivimab and etesevimab are both available as solutions in separate vials and must be diluted and combined prior to administration.
- **To prepare the dose you will need 1 vial of bamlanivimab and 2 vials of etesevimab.**
- Administer bamlanivimab and etesevimab together as a single IV infusion via pump or gravity
- Clinically monitor during administration and observe for at least 1 hour after infusion is complete.

Efficacy²: Support for this EUA is based on data from the Phase 2/3 BLAZE-1 trial ([NCT04427501](#)) and the Phase 2 BLAZE-4 trial ([NCT04634409](#)). BLAZE-1 provides clinical efficacy data from subjects receiving 2800 mg bamlanivimab and 2800 mg of etesevimab together. BLAZE-4 provides comparative virologic outcome data from subjects receiving 700 mg bamlanivimab and 1400 mg etesevimab (the authorized doses), subjects receiving 2800 mg bamlanivimab and 2800 mg of etesevimab, and placebo.

BLAZE-1 Trial: Phase 3 data (N=518 patients receiving 2800 mg bamlanivimab and 2800 mg of etesevimab)

- Primary endpoint: proportion of COVID-19 related hospitalization or death by any cause by Day 29.
- Events occurred in 36 subjects treated with placebo (7%) as compared to 11 events in subjects treated with bamlanivimab 2800 mg and etesevimab 2800 mg together (2%) [$p < 0.001$], a 70% risk reduction.
- There were 10 deaths in subjects treated with placebo and no deaths in subjects treated with bamlanivimab 2800 mg and etesevimab 2800 mg together ($p < 0.001$).

BLAZE-4 Trial: Phase 2 data

- Subjects treated with bamlanivimab 700 mg and etesevimab 1400 mg (N=158), bamlanivimab 2800 mg and etesevimab 2800 mg (N=101), bamlanivimab alone at 700 mg (N=103), or placebo (N=153).
- Primary endpoint: proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7
- The rates were:
 - 31% (42/135) for placebo,
 - 14% (21/147, $p < 0.001$ vs placebo) for bamlanivimab 700 mg and etesevimab 1400 mg together,
 - 10% (10/99, $p < 0.001$ vs placebo) for bamlanivimab 2800 mg and etesevimab 2800 mg together

Based on analyses of the available nonclinical, clinical, and virologic data, as well as supportive data from pharmacokinetic/ pharmacodynamic modeling, the authorized dosage of 700 mg bamlanivimab and 1400 mg etesevimab is expected to have similar clinical effect to 2800 mg bamlanivimab and 2800 mg etesevimab.

Safety / Adverse Drug Events²:

Approximately 1500 subjects have been exposed to bamlanivimab and etesevimab administered together in clinical trials in ambulatory (non-hospitalized) subjects at doses of bamlanivimab 700 mg and etesevimab 1400 mg or higher. *Bamlanivimab and etesevimab at the authorized doses (700 mg and 1400 mg) have been administered together to approximately 770 subjects.* Adverse events from BLAZE-1 (Phase 3) occurred in 13% of subjects who received 2800 mg of bamlanivimab and 2800 mg etesevimab together, and in 12% of placebo-treated subjects. The most common adverse events were nausea, dizziness, and rash. These events occurred in 1% of subjects treated with bamlanivimab and etesevimab and in 1% of placebo subjects. Additionally, 1% of subjects treated with the combination experienced hypersensitivity events, including 2 infusion-related reactions (moderate severity), 2 cases of rash (1 mild, 1 moderate), 1 infusion site rash (mild), and 1 case of pruritus. All events resolved.

Mandatory Requirements under the EUA¹⁻³:

1. Use bamlanivimab and etesevimab only in authorized patient populations described above
2. Communicate to patients or parents/caregivers, as age appropriate, information consistent with the [“Fact Sheet for Patients, Parents and Caregivers”](#) prior to patient receiving bamlanivimab and etesevimab. **Healthcare providers** (to the extent practicable given the circumstances of the emergency) **must document in the patient’s medical record that the patient/caregiver has been:**
 - *Given the “Fact Sheet for Patients, Parents and Caregivers”,*
 - *Informed of alternatives to receiving authorized bamlanivimab and etesevimab, and*
 - *Informed that bamlanivimab and etesevimab are unapproved drugs authorized for use under this EUA.*
3. Avoid use in patients with known hypersensitivity to any ingredient of bamlanivimab and etesevimab
4. The prescriber is responsible for mandatory reporting of all drug errors and serious adverse events potentially related to casirivimab/imdevimab treatment within 7 calendar days from onset of event.
 - *Should include the words “use of bamlanivimab and etesevimab was under EUA” in the “Describe Event” section*
 - *Should include the words “Indian Health Service” or “IHS” on the form in the reporter section (section G)*
 - Information on the FDA MedWatch program can be found on the [IHS Pharmacovigilance website](#).

References:

1. U.S. Food and Drug Administration. [Letter of Authorization](#). Emergency Use Authorization (EUA) of bamlanivimab and etesevimab.
2. U.S. Food and Drug Administration. [Fact Sheet for Health Care Providers](#). Emergency Use Authorization (EUA) of bamlanivimab and etesevimab.
3. U.S. Food and Drug Administration. [Fact Sheet for Patients, Parents and Caregivers](#). Emergency Use Authorization of bamlanivimab and etesevimab.