NEW DRUG APPROVAL

Brand Name	N/A
Generic Name	bamlanivimab and etesevimab
Drug Manufacturer	Eli Lilly and Company

New Drug Approval

FDA Approval Date: February 9, 2021 - **Emergency Use Authorization Only**

Review Designation: N/A

Type of Review: Emergency Use Authorization (EUA)

Dispensing Restrictions: Bamlanivimab and etesevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus (SARS-CoV-2). Most people infected with the COVID-19 virus will experience mild to moderate respiratory illness and recover without requiring special treatment. Older people, and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness. The COVID-19 virus spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes, so it's important that you also practice respiratory etiquette (for example, by coughing into a flexed elbow).

In December 2019, pneumonia of unknown cause occurred in Wuhan (China). On January 7, 2020, a novel corona virus, named as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), was identified in the throat swab sample of 1 patient. Globally, over 55 million confirmed cases of COVID-19 have been reported in all continents except Antarctica.

Efficacy

The data supporting this EUA are based on analyses of data from the Phase 2/3 BLAZE1 trial (NCT04427501) and the Phase 2 BLAZE-4 trial (NCT04634409). Both trials are evaluating the safety and efficacy of bamlanivimab and etesevimab together for treatment of subjects with mild to moderate COVID-19. BLAZE-1 provides clinical efficacy data from subjects receiving 2,800 mg bamlanivimab and 2,800 mg of etesevimab together. BLAZE-4 provides comparative virologic outcome data from subjects receiving 700 mg bamlanivimab and 1,400 mg etesevimab (the authorized doses), subjects receiving 2,800 mg bamlanivimab and 2,800 mg of etesevimab, and placebo.

BLAZE-1 Trial (NCT04427501)

- Phase 2/3, randomized, double-blind, placebo-controlled trial in outpatients with mild to moderate COVID-19 presenting within 3 days of first positive test results who were at high risk of progressing to severe COVID-19 and/or hospitalization
- N = 1,035
- Patients randomized to receive bamlanivimab + etesevimab (2,800 mg of each antibody) or placebo
- Control: Placebo
- Dosing: Single IV infusion
- Endpoint: COVID-19-related hospitalization or death

- Results of analysis:
  - Events: 2.1% treatment group, 7.0% placebo group (P = 0.0004)
  - Deaths: 0 treatment group, 10 placebo group (P <0.001)
  - Significant improvements in all key secondary endpoints such as reduced viral load and accelerated symptom resolution
  - 70% risk reduction in rate of hospitalization and deaths

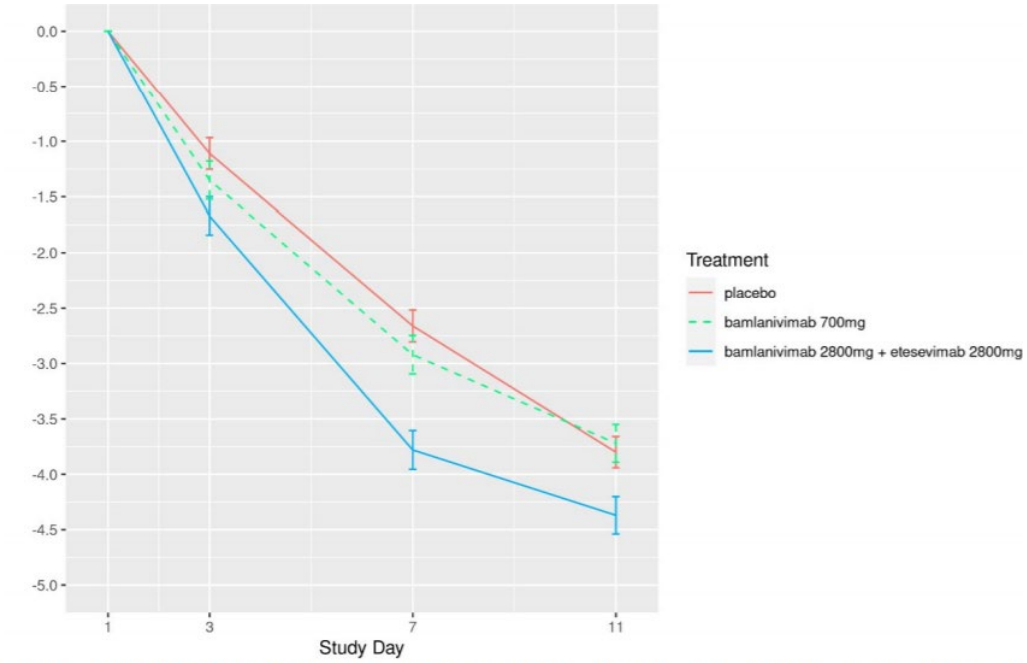

Figure 1: SARS-CoV-2 Viral Load Change from Baseline by Visit from the Phase 2 Portion of BLAZE-1.

BLAZE-4 Trial (NCT04634409)
Initial results from this study provided viral load and pharmacodynamic-pharmacokinetic data that demonstrated bamlanivimab 700 mg and etesevimab 1,400 mg together are similar to bamlanivimab 2,800 mg and etesevimab 2,800 mg together.

Safety

ADVERSE EVENTS

Bamlanivimab and etesevimab together:

- Based on Phase 2 data from BLAZE-1, nausea was the most commonly reported adverse event, reported by 4% of subjects in both bamlanivimab and etesevimab together and placebo groups. Pruritus and pyrexia were more frequently reported from subjects treated with both bamlanivimab and etesevimab (2% and 1%) compared to placebo (1% and 0%, respectively).
- Based on Phase 3 data from BLAZE-1, the most common adverse events were nausea, dizziness, and rash. These events each occurred in 1% of subjects treated with bamlanivimab and etesevimab together and in 1% of placebo subjects.

WARNINGS & PRECAUTIONS

- **Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions**: Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of bamlanivimab with and without

etesevimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy.

- **Clinical Worsening After Bamlanivimab Administration**: 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.
- **Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19:** 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.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Bamlanivimab is a recombinant neutralizing human IgG1κ monoclonal antibody (mAb) to the spike protein of SARS-CoV-2 and is unmodified in the Fc region. Bamlanivimab binds the spike protein with a dissociation constant KD = 0.071 nM and blocks spike protein attachment to the human ACE2 receptor with an IC50 value of 0.17 nM (0.025 µg/mL).

Etesevimab is a recombinant neutralizing human IgG1κ mAb to the spike protein of SARS-CoV-2, with amino acid substitutions in the Fc region (L234A, L235A) to reduce effector function. Etesevimab binds the spike protein with a dissociation constant KD = 6.45 nM and blocks spike protein attachment to the human ACE2 receptor with an IC50 value of 0.32 nM (0.046 µg/mL).

Bamlanivimab and etesevimab bind to different but overlapping epitopes in the receptor binding domain (RBD) of the S-protein. Using both antibodies together is expected to reduce the risk of viral resistance.

Dose & Administration

ADULTS

The optimal dosing regimen for treatment of COVID-19 has not yet been established. The recommended dosing regimen may be updated as data from clinical trials become available.

The dosage of bamlanivimab and etesevimab 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) is:

- bamlanivimab 700 mg
- etesevimab 1,400 mg.

Administer bamlanivimab and etesevimab together as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset. Under this EUA, bamlanivimab and etesevimab must be diluted and administered together as a single intravenous infusion.

PEDIATRICS

No dosage adjustment is recommended in pediatric patients who weigh at least 40 kg and are 12 years of age and older. Bamlanivimab and etesevimab are not authorized for patients weighing less than 40 kg or those less than 12 years of age.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None.

HEPATIC IMPAIRMENT

None.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Intravenous vial (ml): 700 mg/20 ml (35 mg/ml)