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An EUA for Bamlanivimab and Etesevimab for COVID-19

Revised 1/6/2022: The Variants paragraph has been updated. See also COVID-19 Updates.

Revised 9/23/2021: As of September 2, 2021, distribution of bamlanivimab and etesevimab has resumed in all US jurisdictions (https://bit.ly/3AynAdr).

The FDA has issued an Emergency Use Authorization (EUA) for Lilly's investigational monoclonal antibodies bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016) to be administered together for treatment of mild to moderate COVID-19 in patients ≥12 years old who weigh ≥40 kg and are at high risk of progressing to severe disease and/or hospitalization (see Table 1).[1] Bamlanivimab received an EUA for use as monotherapy in such patients in November 2020.[2] Regeneron's investigational monoclonal antibodies casirivimab (REGN10933) and imdevimab (REGN10987) are also authorized for use together for the same indication.[3]

Pronunciation Key
Bamlanivimab: bam" la ni' vi mab
Etesevimab: eh" teh se' vi mab

Use of monoclonal antibodies has been associated with worse clinical outcomes in hospitalized patients with COVID-19 who require high-flow oxygen or mechanical ventilation. Bamlanivimab and etesevimab are not authorized for use in patients who are hospitalized for COVID-19 or require oxygen therapy because of COVID-19.

MECHANISM OF ACTION — Bamlanivimab and etesevimab bind to different but overlapping sites on the receptor binding domain of the spike protein of SARS-CoV-2, blocking its attachment to the human ACE2 receptor.

CLINICAL STUDIES — Issuance of the EUA for bamlanivimab and etesevimab was based on the results of two randomized, double-blind trials in outpatients with mild to moderate COVID-19.

The first trial (BLAZE-1) had a phase 2 and a phase 3 component. In the phase 2 component, 612 adult patients (42% high risk) received a single infusion of bamlanivimab 2800 mg plus etesevimab 2800 mg, bamlanivimab alone (700 mg, 2800 mg, or 7000 mg), or placebo. The mean decrease from baseline in log SARS-CoV-2 viral load at day 11, the primary endpoint, was significantly greater with bamlanivimab plus etesevimab than with placebo (-4.37 vs -3.80). None of the doses of bamlanivimab alone significantly reduced viral load at day 11 compared to placebo.[4]

In the phase 3 component of BLAZE-1 (unpublished; summarized in the FDA Fact Sheet), 1035 high-risk adults received either bamlanivimab 2800 mg plus etesevimab 2800 mg or placebo. The primary endpoint, hospitalization due to COVID-19 or death from any cause by day 29, occurred significantly less often with the antibodies than with placebo (2.1% vs 6.6%; HR 0.32; NNT 22.5). No deaths occurred in the antibody group, compared to 10 in the placebo group ($p < 0.001$).[5,6]

In the second trial (BLAZE-4; unpublished; summarized in the FDA Fact Sheet), 259 patients 18-65 years old with a BMI <35 kg/m^2 received either bamlanivimab 2800 mg plus etesevimab 2800 mg or bamlanivimab 700 mg plus etesevimab 1400 mg. The mean change in SARS-CoV-2 viral load was similar with the two doses of the

Table 1. Eligible Patients Considered High-Risk[1]

Patients with ≥1 of the following:
- ≥65 years old
- BMI ≥35
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease
- Currently receiving immunosuppressive treatment

Patients ≥55 years old with ≥1 of the following:
- Cardiovascular disease
- Hypertension
- COPD or other chronic respiratory disease

Patients 12-17 years old with ≥1 of the following:
- BMI ≥85th percentile for their age and gender[2]
- Sickle cell disease
- Congenital or acquired heart disease
- Neurodevelopmental disorders (e.g., cerebral palsy)
- A medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID-19])
- Asthma, reactive airway or other chronic respiratory disease that requires daily drug treatment

BMI = body mass index; COPD = chronic obstructive pulmonary disease
1. Adult and pediatric patients (≥12 years old and weighing ≥40 kg) with ≥1 of the criteria listed are considered at high risk for progressing to severe COVID-19 and/or hospitalization. (FDA. Fact sheet for health care providers. Emergency Use Authorization (EUA) of bamlanivimab and etesevimab. Available at: https://bit.ly/3qfS6DN. Accessed March 18, 2021).
2. Based on CDC growth charts (https://bit.ly/36U0twf).

combination. The FDA selected 700 mg/1400 mg as the authorized dose for use of bamlanivimab and etesevimab together, which prompted the manufacturer to study this dosage in a new cohort of BLAZE-1.[5]

In the new BLAZE-1 cohort (unpublished; summarized in a press release), 769 high-risk patients ≥12 years old received either bamlanivimab 700 mg plus etesevimab 1400 mg or placebo. The rate of hospitalization due to COVID-19 or death from any cause by day 29 was significantly lower with the antibodies than with placebo (0.8% vs 5.4%; HR 0.13; NNT 21.5). No deaths occurred in the antibody group, compared to 4 in the placebo group.[6]

No studies directly comparing bamlanivimab and etesevimab with casirivimab and imdevimab are available.

VARIANTS — In BLAZE-1, treatment-emergent SARS-CoV-2 variants developed less frequently in patients who received bamlanivimab plus etesevimab than in those who received bamlanivimab alone. The combination is not active against the Omicron variant of SARS-CoV-2. It retains activity against the Delta variant of the virus.[5]

ADVERSE EFFECTS — Hypersensitivity reactions including anaphylaxis have been reported with use of bamlanivimab with and without etesevimab.

DOSAGE AND ADMINISTRATION — Bamlanivimab and etesevimab are supplied separately in 700 mg/20 mL vials, but when used together, they must be administered as a single IV infusion; the authorized dose is 700 mg (one vial) of bamlanivimab and 1400 mg (two vials) of etesevimab. The antibodies should be diluted in 50, 100, 150, or 250 mL of normal saline and infused at a maximum rate of 310 mL/hr (266 mL/hr when mixed with 250 mL normal saline for patients weighing <50 kg) immediately after preparation. If immediate use is not possible, the solution can be refrigerated for up to 24 hours or left at room temperature for up to 7 hours, including infusion time. If refrigerated, the solution should be allowed to sit at room temperature for 20 minutes before use.

Bamlanivimab and etesevimab should be administered as soon as possible after a positive SARS-CoV-2 test result and within 10 days of COVID-19 symptom onset. Patients should be treated in a facility staffed and equipped to manage anaphylaxis and they should be monitored for hypersensitivity reactions during administration of the drug and for at least 1 hour after completion of the infusion.

AVAILABILITY — Bamlanivimab and etesevimab will be allocated to state health departments by the US Department of Health and Human Services (HHS) based on case counts and severity of outbreaks. State health departments will then be responsible for allocating the antibodies to local health facilities. The manufacturer plans to produce 1 million doses of etesevimab for use with bamlanivimab by mid-2021.[7]

CONCLUSION — The FDA has issued an Emergency Use Authorization (EUA) for the monoclonal antibodies bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016) to be administered together by IV infusion for treatment of mild to moderate COVID-19. Administration of the antibodies to high-risk outpatients recently diagnosed with COVID-19 reduced viral load and decreased the risk of hospitalization and death. Compared to bamlanivimab alone, use of the combination appears to be more effective in reducing viral load and less likely to result in development of treatment-emergent variants. How bamlanivimab and etesevimab compare with casirivimab (REGN10933) and imdevimab (REGN10987), two other monoclonal antibodies available for use together through an EUA, remains to be determined. ■

1. FDA News Release. Coronavirus (COVID-19) update: FDA authorizes monoclonal antibodies for treatment of COVID-19. February 9, 2021. Available at: http://bit.ly/3d8grHG. Accessed Accessed March 18, 2021.
2. An EUA for bamlanivimab – a monoclonal antibody for COVID-19. Med Lett Drugs Ther 2020; 62:185.
3. An EUA for casirivimab and imdevimab for COVID-19. Med Lett Drugs Ther 2020; 62:201.
4. RL Gottlieb et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA 2021; 325:632.
5. FDA. Fact sheet for health care providers. Emergency Use Authorization (EUA) of bamlanivimab and etesevimab. Available at: https://bit.ly/3qfS6DN. Accessed January 6, 2021.
6. Lilly News Release. Lilly's bamlanivimab and etesevimab together reduced hospitalizations and death in phase 3 trial for early COVID-19. March 10, 2021. Available at: http://bit.ly/2PRZmZ7. Accessed March 18, 2021.
7. Lilly News Release. Lilly's bamlanivimab (LY-CoV555) administered with etesevimab (LY-CoV016) receives FDA emergency use authorization for COVID-19. February 9, 2021. Available at: http://bit.ly/3jGYIbM. Accessed March 18, 2021.

Online Tables: COVID-19 Treatments and Vaccines

Please check our website for the latest information on COVID-19, including our continuously updated tables: Treatments Considered for COVID-19 and COVID-19 Vaccine Comparison Chart. Available at: www.medicalletter.org/drugs-for-covid-19.

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COVID-19 UPDATES

Pfizer-BioNTech COVID-19 Vaccine

On January 3, the FDA amended its Emergency Use Authorization (EUA) for the Pfizer-BioNTech COVID-19 vaccine *(Comirnaty)* to incorporate the following changes:

1. A third primary dose of the vaccine can now be given ≥28 days after the second to children 5-11 years old who have undergone solid organ transplantation or have an equivalent level of immune compromise.[1,2]
2. Booster doses of the vaccine are now authorized for use in children 12-15 years old.[1,3]
3. The length of time after completion of a primary series with the vaccine at which patients become eligible for booster immunization has been reduced from 6 months to 5 months.[1,3]

On January 7, the FDA amended the EUA of the Moderna COVID-19 vaccine to shorten the interval between completion of a primary series and receipt of a booster dose from 6 months to 5 months.[4]

Booster Schedules – Patients can now receive a booster dose of a COVID-19 vaccine 5 months after completion of a primary series with the Pfizer-BioNTech or Moderna vaccine or 2 months after receiving a primary dose of the Johnson & Johnson/Janssen vaccine. ■

1. FDA News Release. Coronavirus (COVID-19) update: FDA takes multiple actions to expand use of Pfizer-BioNTech COVID-19 vaccine. January 3, 2022. Available at: https://bit.ly/3qVaN18. Accessed January 6, 2022.
2. FDA. Fact sheet for health care providers administering vaccine (vaccination providers). Emergency Use Authorization (EUA) of the Pfizer-BioNTech COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19). For 5-11 years of age. January 3, 2022. Available at: https://bit.ly/3jX9xri. Accessed January 6, 2022.
3. FDA. Fact sheet for health care providers administering vaccine (vaccination providers). Emergency Use Authorization (EUA) of the Pfizer-BioNTech COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19). For 12 years of age and older. January 3, 2022. Available at: https://bit.ly/3bBH5GV. Accessed January 6, 2022.
4. FDA. Fact sheet for healthcare providers administering vaccine (vaccination providers). Emergency Use Authorization (EUA) of the Moderna COVID-19 vaccine to prevent coronavirus disaese 2019 (COVID-19). January 7, 2022. Available at: https://bit.ly/3nosylA. Accessed January 7, 2022.

Monoclonal Antibodies for COVID-19

The anti-SARS-CoV-2 antibody combinations casirivimab plus imdevimab *(REGEN-COV)* and bamlanivimab plus etesevimab are not active against the Omicron variant of SARS-CoV-2. These antibodies remain available, however, through federal distribution. NIH guidelines state that their use can be considered in regions where the Delta variant still causes a significant proportion of COVID-19 cases if alternative drugs are unavailable or contraindicated.[1,2]

Sotrovimab, which is authorized by the FDA for treatment of mild to moderate COVID-19 in patients ≥12 years old who weigh ≥40 kg and are at high risk of progressing to severe disease, is the only monoclonal antibody available in the US that has activity against the Omicron variant of SARS-CoV-2.[2,3] ■

1. HHS Public Health Emergency. Updated guidelines regarding allocation of bamlanivimab/etesevimab and REGEN-COV therapeutics: states and territories can continue to order both products. December 31, 2021. Available at: https://bit.ly/3sZHD3o. Accessed January 6, 2022.
2. NIH. The COVID-19 Treatment Guidelines Panel's statement on therapies for high-risk, nonhospitalized patients with mild to moderate COVID-19. December 30, 2021. Available at: https://bit.ly/3EUXjHz. Accessed January 6, 2022.
3. An EUA for sotrovimab for treatment of COVID-19. Med Lett Drugs Ther 2021; 63:97.

Additional Content Available Online: COVID-19 Charts

More information on vaccines and drugs for COVID-19 can be found in the COVID-19 Resources section of our website: www.medicalletter.org/drugs-for-covid-19.

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