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Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
U.S.A.

Lilly's statement on the FDA's Fact Sheet update for bamlanivimab and etesevimab to include a new Limitation for Authorized Use

Lilly continually monitors the COVID-19 environment and is committed to ensuring our antibodies are available, as appropriate, to patients as variants continue to evolve and their patterns of transmission and prevalence shift.

The FDA has updated the Fact Sheet for bamlanivimab and etesevimab to include a new Limitation for Authorized Use: due to the high frequency of the Omicron variant, these therapies are not currently authorized in any U.S. region.

Lilly and the FDA agree that it is not medically appropriate, at this time, to treat patients with mild to moderate COVID-19 with bamlanivimab and etesevimab together in the U.S. Evaluation of both pseudovirus and authentic virus confirm that they are not effective at treating the currently predominant Omicron variant. Authorization status will change as needed, depending on prevalence and trends of variants of concern.

Authentic virus analysis of Lilly's third investigational antibody therapy, bebtelovimab, confirm our earlier pseudovirus findings, which demonstrate our investigational antibody potently inactivates all known variants of concern, including Omicron. We are working urgently with the FDA to potentially bring bebtelovimab to patients through emergency use authorization. FDA review of the bebtelovimab submission is ongoing.

Important Information about bamlanivimab and etesevimab together

- Bamlanivimab and etesevimab together have not been approved, but have been authorized for emergency use by the FDA.

- Bamlanivimab and etesevimab together are authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of bamlanivimab and etesevimab under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

Authorized Use

TREATMENT

Bamlanivimab and etesevimab are authorized to be administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients, including neonates, 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: Treatment

- Bamlanivimab and etesevimab are not authorized for treatment of mild to moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency.
    - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs. [1]
- Bamlanivimab and etesevimab are not authorized for use in patients 2 years and older who are hospitalized due to COVID-19[2]
- Bamlanivimab and etesevimab are not authorized for use in patients, regardless of age, who:
    - require oxygen therapy and/or respiratory support due to COVID-19, OR
    - require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 and are on chronic oxygen therapy and/or respiratory support 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

Bamlanivimab and etesevimab administered together are authorized in adults and pediatric individuals, including neonates, for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[3] **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[4]) **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)[5] **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, prisons).

Limitations of Authorized Use: Post-Exposure Prophylaxis

- Bamlanivimab and etesevimab are not authorized for post-exposure prophylaxis of COVID-19 in geographic regions where exposure is likely to have been to a non-susceptible SARS-CoV-2 variant, based on available information including variant susceptibility to these drugs and regional variant frequency.
    - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs
- Post-exposure prophylaxis with bamlanivimab and etesevimab is not a substitute for vaccination against COVID-19.
- Bamlanivimab and etesevimab together are not authorized for pre-exposure prophylaxis for prevention of COVID-19.

IMPORTANT SAFETY INFORMATION

There are limited clinical data available for bamlanivimab and etesevimab. Serious and unexpected adverse events may occur that have not been previously reported with the use of bamlanivimab and etesevimab together.

WARNINGS

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of bamlanivimab and 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.

Infusion-related reactions, occurring during the infusion and up to 24 hours after 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 etesevimab under Emergency Use Authorization.

Clinical Worsening After Bamlanivimab and Etesevimab Administration

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.

Limitations of Benefit and Potential 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. See Limitations of Authorized Use.

Adverse Reactions

Adverse reactions observed in those who have received bamlanivimab and etesevimab are anaphylaxis (n=1, 0.07%) and infusion-related reactions (n=16, 1.1%). The most common treatment-emergent adverse events included nausea, dizziness, and pruritis. No treatment-emergent events occurred in more than 1% of participants and rates were comparable to placebo.

USE IN SPECIFIC POPULATIONS

Pregnancy

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Bamlanivimab and etesevimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Breastfeeding

There are no available data on the presence of bamlanivimab or etesevimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Healthcare providers should review the Fact Sheet for Healthcare Providers for information on the authorized use of bamlanivimab and etesevimab and mandatory requirements of the EUA. Please also see the FDA Letter of Authorization and the Fact Sheet for Patients, Parents and Caregivers on the authorized use of bamlanivimab and etesevimab.

[1] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility *[see Microbiology/Resistance Information (15)]*, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

[2] The reasons for hospital admission may be different and the threshold for hospital admission may be lower for neonates, young infants and toddlers with COVID-19 compared to older children and adults. The authorization allows for young children (i.e., birth to 2 years of age) who are hospitalized with mild to moderate COVID-19 at the time of treatment to receive bamlanivimab and etesevimab.

[3] Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated.

[4] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html.

[5] Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html.