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Lilly's statement on FDA's de-authorization of bebtelovimab in the U.S.

Given the combined proportion of COVID-19 cased caused by the Omicron BQ.1 and BQ.1.1 variants, the U.S. Food and Drug Administration (FDA) has announced bebtelovimab is not currently authorized for emergency use treatment of mild-to-moderate COVID-19 in adults and pediatric patients. Lilly and the FDA agree that it is not medically appropriate, at this time, to treat high-risk patients with mild-to-moderate COVID-19 with bebtelovimab in the US.

Based on pseudovirus data, Lilly can confirm that bebtelovimab does not retain neutralization activity against the BQ.1 and BQ.1.1 variants, most likely due to an amino acid K444T substitution. Lilly will pause all distribution of bebtelovimab. Any unused bebtelovimab may be kept during the pause—please follow storage and handling as specified in the Fact Sheet.

As we have seen over the last several months, prevalence of COVID variant sublineages vary by state, region and even country, and can change rapidly. Lilly continually monitors the global COVID-19 environment, assessing the neutralization activity of potential antibody therapies against a wide array of existing and emerging mutations and variants. Lilly will continue to search and evaluate monoclonal antibodies to identify potential candidates for clinical development against new variants.

Important Information about bebtelovimab

Bebtelovimab has not been approved, but has been authorized for emergency use by the FDA under an EUA, 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 and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

The emergency use of bebtelovimab is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21

U.S.C. § 360bbb3(b)(1), unless the declaration is terminated or authorization is revoked sooner.

Healthcare providers should review the Fact Sheet for Healthcare Providers for information on the authorized use of bebtelovimab 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 bebtelovimab. [2]

Authorized Use and Important Safety Information

Bebtelovimab is authorized for use under Emergency Use Authorization (EUA) 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[i] for progression to severe COVID-19, including hospitalization or death, **and**
- for whom alternate COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

LIMITATIONS OF AUTHORIZED USE

Bebtelovimab is 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 this drug and regional variant frequency.

- 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, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.
- 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
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Bebtelovimab is not authorized for use in patients who:

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

IMPORTANT SAFETY INFORMATION The following provides essential safety information on the unapproved use of bebtelovimab under the Emergency Use Authorization.

WARNINGS AND PRECAUTIONS
There are limited clinical data available for bebtelovimab. Serious and unexpected adverse events may occur that have not been previously reported with bebtelovimab use.

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions
Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of other SARS-CoV-2 monoclonal antibodies and could occur with administration of bebtelovimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration, and initiate appropriate medications and/or supportive care.

Infusion-related reactions, which may occur up to 24 hours after the injection, have been observed in clinical trials of bebtelovimab when administered with other monoclonal antibodies and may occur with use of bebtelovimab alone. 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. presyncope, syncope), dizziness, and diaphoresis.

Administer appropriate medications and/or supportive care if an infusion-related reaction occurs.

Hypersensitivity reactions occurring more than 24 hours after the injection have also been reported with the use of SARS-CoV-2 monoclonal antibodies under Emergency Use Authorization.

Clinical Worsening After Monoclonal Antibody Administration
Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment 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 SARS-CoV-2 monoclonal antibody use or were due to progression of COVID-19.

Limitations of Benefit and Potential Risk in Patients with Severe COVID-19
Treatment with bebtelovimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bebtelovimab, 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 bebtelovimab, alone or in combination with bamlanivimab and etesevimab, at the authorized dose or higher, are infusion-related reactions (n=2, 0.3%), pruritus (n=2, 0.3%) and rash (n=5, 0.8%). The most common treatment-emergent adverse events observed in subjects treated with bebtelovimab, alone or in combination with bamlanivimab and etesevimab, at the authorized dose or higher, included nausea (0.8%) and vomiting (0.7%).

USE IN SPECIFIC POPULATIONS
Pregnancy
Severe hypersensitivity reactions and infusion-related reactions, have been observed with administration of bebtelovimab, including in pregnant patients. Pregnant patients who develop severe hypersensitivity and infusion-related reactions should be managed appropriately, including obstetrical care. There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Bebtelovimab 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 bebtelovimab 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.

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[i.] For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. Healthcare providers should consider the benefit-risk for an individual patient