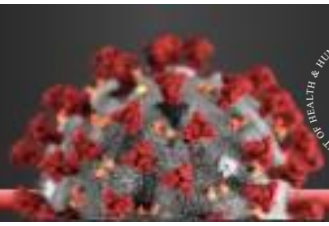
Indian Health Service
National Pharmacy and Therapeutics Committee

COVID-19 Emerging Treatments Update



February 14, 2022

** Emergency Use Authorization **

New Monoclonal Antibody for Treatment of COVID-19 that Retains Activity Against Omicron Variant: bebtelovimab

Background & Current Status[1,2]:

On February 11, 2022, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for a new monoclonal antibody for the treatment of COVID-19 that retains activity against the Omicron variant. The EUA for bebtelovimab is for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kilograms, which is about 88 pounds) with a positive COVID-19 test, 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 the FDA are not accessible or clinically appropriate**.

Limitations of authorized use:

Bebtelovimab is not authorized for patients who are hospitalized due to COVID-19 or require oxygen therapy due to 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.

Bebtelovimab is **NOT authorized** for use in the following patient populations:

- Adults or pediatric patients who are hospitalized due to COVID-19, or
- Adults or pediatric patients who require oxygen therapy and/or respiratory support due to COVID-19, or
- Adults or pediatric patients who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen therapy and/or oxygen support due to underlying non-COVID-19-related comorbidity;

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 these drugs and regional variant frequency.

Availability[2]:

Distribution of the authorized bebtelovimab will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. The manufacturer will supply bebtelovimab to authorized distributor(s) who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed. The IHS National Supply Service Center anticipates that ordering will be available for IHS facilities in a limited capacity during the month of February 2022.

Vaccine Efficacy & Safety Data[2,3]:

The data supporting this EUA for treatment of mild-to-moderate COVID-19 are primarily based on analyses of data from the Phase 2 portion of the BLAZE-4 trial (NCT04634409). This trial evaluated the clinical efficacy data from subjects receiving 175 mg bebtelovimab alone and together with 700 mg bamlanivimab and 1,400 mg of etesevimab. BLAZE-4 is a Phase 1/2, randomized, single-dose clinical trial evaluating treatment of subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). Efficacy of bebtelovimab, alone and together with bamlanivimab and etesevimab, was evaluated in low risk adults (i.e., those not at high-risk to progress to severe COVID-19) in a randomized part of the trial which included a placebo control arm.

The trial enrolled subjects who were not hospitalized and had 1 or more COVID-19 symptoms that were at least mild in severity. Treatment was initiated within 3 days of obtaining the clinical sample for the first positive SARS-CoV-2 viral infection determination. **BLAZE-4 was conducted prior to the emergence of the Omicron variant. No subject in BLAZE-4 was infected with virus of the Omicron lineage or sub-lineages. The majority of participants in the trial were infected with Delta (49.8%) and Alpha (28.6%).**

(1) Phase 2 Data from the Placebo-Controlled Portion of BLAZE-4 (Low Risk Subjects)
In this portion of the trial, adult subjects were treated with a single infusion of bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg (N=127), 175 mg bebtelovimab alone (N=125), or placebo (N=128). The primary endpoint was the proportion of subjects with persistently high viral load (PHVL) by Day 7.

PHVL occurred in 26 subjects with placebo (21%) as compared to 16 (13%) subjects treated with bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg together [p=0.098], and 17 (14%) subjects treated with bebtelovimab 175 mg alone [p=0.147], a 38% (95% CI: -9%, 65%) and 34% (95% CI: -15%, 62%) relative reduction, respectively.

(2) Phase 2 Data from the Randomized, Open-Label Portion of BLAZE-4 (High Risk Subjects)
In this portion of the trial, subjects were treated with a single infusion of bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg (N=50) or 175 mg bebtelovimab alone (N=100). The majority (91.3%) of the subjects enrolled in these dose arms meet the criteria for high-risk.

The primary objective for these treatment arms was to characterize the safety profile of bebtelovimab 175 mg by evaluating adverse events and serious adverse events. Efficacy endpoints included the proportion of subjects with COVID-19 related hospitalization or death by any cause by Day 29, mean change in viral load from baseline to Days 3, 5, 7, and 11 and time to sustained symptom resolution. The proportion of subjects with COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause was assessed by Day 29. Events occurred in 2 (4%) subjects treated with bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg together and 3 (3%) subjects treated with bebtelovimab 175 mg alone. There was 1 subject treated with bebtelovimab 175 mg alone who died on Day 34.

(3) Phase 2 Data from the Non-Randomized, Open-Label Portion of BLAZE-4 (High Risk Subjects)
In this portion of the trial, subjects were treated with a single infusion of bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg (N=176). The primary objective for this arm was to characterize the safety profile of bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg by evaluating adverse events and serious adverse events.

Efficacy endpoints included the proportion of subjects with COVID-19 related hospitalization or death by any cause by Day 29, mean change in viral load from baseline to Days 3, 5, 7, and 11, and time to sustained symptom resolution. The proportion of subjects with COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause was assessed by Day 29. Events occurred in 3 subjects (1.7%), and no subjects died. Mean changes in viral load from baseline to Day 3, 5, 7, and 11 were -1.4, -3.1, -4.0, and -5.4, respectively. The median time to sustained symptom resolution as recorded in a trial specific daily symptom diary was 8 days.

Current EUA Fact Sheets[3,4]:

As a convenience, Fact Sheets for Bebtelovimab are accessible below:

- Healthcare Providers -OR- Patients, Parents and Caregivers

Conditions of Authorization for Healthcare Facilities under the Emergency Use Authorization[2]:

- Ensure that healthcare facilities are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients and caregivers, respectively, through appropriate means, prior to administration of bebtelovimab
- Track all serious adverse events and medication errors potentially related to bebtelovimab and report these to FDA. Complete and submit a MedWatch form or complete and submit FDA Form 3500 by fax (1-800-FDA-0178). Submitted reports must state, "Bebtelovimab use for COVID-19 under EUA" at the beginning of the question "Describe Event" for further analysis. ***Federal, Tribal, and Urban programs are all encouraged to put "IHS" into field #26 of the form.***
- Ensure that appropriate storage is maintained until the product is administered consistent with the terms of this letter and the authorized labeling.
- Maintain records regarding the dispensing and administration of bebtelovimab for the use authorized in this letter (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered)
- Ensure that any records associated with this EUA are maintained until notified by Lilly and/or FDA. Such records will be made available to Lilly, HHS, and FDA for inspection upon request.
- Report therapeutics information and utilization data as directed by HHS

References:

1. Food and Drug Administration. FDA News Release. Coronavirus (COVID-19) Update: FDA Authorizes New Monoclonal Antibody for Treatment of COVID-19 that Retains Activity Against Omicron Variant. Published February 11, 2022.
2. Food and Drug Administration. Bebtelovimab Letter of Authorization. Issued February 11, 2022.
3. Food and Drug Administration. Bebtelovimab: FACT SHEET FOR HEALTHCARE PROVIDERS. Released February 11, 2022.
4. Food and Drug Administration. Bebtelovimab: FACT SHEET FOR PATIENTS, PARENTS & CAREGIVERS. Released February 11, 2022.