Emergency Use Authorization (EUA) for Bebtelovimab 175 mg

Center for Drug Evaluation and Research (CDER) Memorandum

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)	111
Date of Memorandum	March 25, 2022
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Eli Lilly and Company: Christine Phillips, PhD, RAC Advisor, Global Regulatory Affairs - NA Mobile: (b) (6) Email: phillips_christine_ann@lilly.com
Manufacturer	Eli Lilly and Company
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Proprietary Name	n/a
Established Name/Other names used during development	bebtelovimab (LY-CoV1404)
Dosage Forms/Strengths	bebtelovimab 175 mg IV
Therapeutic Class	SARS-CoV-2 spike protein directed human IgG1κ monoclonal antibody (mAb)
Intended Use or Need for EUA	Treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40kg), 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.
Intended Population(s)	Adults and pediatric patients

Rationale and Revisions to EUA Fact Sheets

On March 21, 2022 Eli Lilly and Company submitted proposed revisions to the HCP Fact Sheets as follows:

- Changes to Section 2.3 Dosage and Administration, Dose Preparation and Administration to the required administration materials based on questions from health care providers (HCPs) regarding the need for the extension sets
- Updates to Table 4 in Section 12.4 Microbiology to Omicron [+R346K] BA.1.1 and P.1 authentic virus data.

Changes to Section 2.3 Dose Preparation and Administration

The change to Section 2.3 to the required administration materials is based on questions from HCPs regarding the need for the extension set as listed in the current fact sheet. Most comments have noted that extension sets for an IV administration of a small volume over at least 30 seconds is not usually required or that extension sets are hard to locate or order. The Department of Veterans Affairs has commented that the difficulty in locating syringe extension sets or significant shipping delays is preventing their sites from using bebtelovimab. The use of syringe extension sets remains the #1 topic the Lilly call center has received regarding bebtelovimab.

In BLAZE-4, the trial included IV administration of larger volumes of 62.5 mL over 6.5 minutes (N= 606) to accommodate the necessary volume of bamlanivimab + etesevimab+ bebtelovimab that were administered in 5 of the treatment arms and 2.5 mL of bebtelovimab over at least 30 seconds (N=100) in arm 12. However, manual administration was allowed for the 2.5 mL administration in arm 12 with the listed extension set. It was not recorded individually if pump or manual administration occurred in the patients that received 2.5 mL. Bebtelovimab 175 mg, as authorized under the EUA, requires only 2 mL volume administered over at least 30 seconds. In the clinical setting, the typical administration of such volumes and over a short time period does not require a syringe pump and therefore does not typically require a syringe extension set.

Standard administration of IV injection of small volumes typically is done by gaining IV access in a patient via a vascular access device that has a short catheter and connection end. Employing standard aseptic technique, the drug-filled

syringe is connected to the vascular access dives for administration followed by a normal saline-filled syringe flush to deliver the entire dose. Syringe extension sets are used to add length between the drug delivery device, such as an infusion or syringe pump, and the vascular access device. However, in clinical practice it is recommended to limit the use of add-on equipment such as extension sets when not needed to decrease the risk of contamination and the potential for errors with connection issues and manipulations.[1]

To address these concerns, Lilly proposed the specify use of a syringe extension set to administer bebtelovimab as optional under the EUA. The language in Section 2.3 Dosage and Administration, Dose Preparation and Administration under Materials Needed for Administration and under Preparation will now read as follows:

Materials Needed for Administration

- 1 bebtelovimab vial (175 mg/2 mL)
- 1 disposable polypropylene dosing syringe capable of holding 2 mL
- 0.9% Sodium Chloride Injection for flushing
- Optional: 1 syringe extension set made of polyethylene or polyvinylchloride with or without di-ethylhexylphthalate (DEHP) ~~syringe extension set~~

Preparation

- Remove bebtelovimab vial from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake vial. Inspect the vial.**
- Withdraw 2 mL from the vial into the disposable syringe.
- Discard any product remaining in the vial.
- This product is preservative-free and therefore, should be administered immediately.
    - If immediate administration is not possible, store the syringe for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) and up to 7 hours at room temperature (20°C to 25°C [68°F to 77°F]). If refrigerated, allow the prepared syringe to equilibrate to room temperature for approximately 20 minutes prior to administration.

[1] Gorski LA, Hadaway L, Hagle ME, et al. Infusion Therapy Standards of Practice, 8th Edition. J Infus Nurs. 2021 Jan-Feb 01;44(1S Suppl 1):S1-S224. doi: 10.1097/NAN.0000000000000396. PMID: 33394637.

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- If used, attach and prime the syringe extension set.
- Administer the entire contents of the syringe via IV injection over at least 30 seconds.
- After the entire contents of the syringe have been administered, **flush the injection line** with 0.9% Sodium Chloride to ensure delivery of the required dose.

Removal of the extension set from administration would not change the route of administration, the rate of administration, or the compatibility of the product with administration materials. Data from addendum 4 of study PYAH evaluating bebtelovimab 175 mg given at 140 mg/min and 350 mg/min did not show any safety risks or increase in infusion-related reactions with increase protein flow rate.

Based on the available data and safety information, as well as understanding of the typical methods of IV administration for products of small volumes over at least 30 seconds in clinical practice, the change to making the syringe extension set optional is reasonable. This change better aligns with current clinical practice and will allow heath care provider flexibility and reduce barriers for treatment of patients.

Changes to Section 12.4 Microbiology

Table 3 in Section 12.4 of the fact sheet is updated to include new authentic SARS-CoV-2 P.1 and BA.1.1 virus isolate data. Additionally, updates to the table footnotes were included to designate which neutralization methodology was used

for each of the variants. The following provides the updates to Table 3.

Table 3: Authentic[a] SARS-CoV-2 Neutralization Data for Bebtelovimab

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested[b]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	No change[c]
B.1.351	South Africa	Beta	K417N, E484K, N501Y	No change[c,d]
P.1	Brazil	Gamma	K417T, E484K, N501Y	No change[c]
B.1.617.2/AY.3	India	Delta	L452R, T478K	No change[c,d]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	No change[c]
B.1.526[de]	USA (New York)	Iota	E484K	No change[c]
B.1.1.529/BA.1	South Africa	Omicron	G339D + S371L + S373P + S375F + K417N + N440K + G446S + S477N + T478K + E484A + Q493R + G496S + Q498R + N501Y + Y505H	No change[c,d]
BA.1.1	South Africa	Omicron [+R346K]	G339D + R346K + S371L + S373P + S375F + K417N + N440K + G446S + S477N + T478K + E484A + Q493R + G496S + Q498R + N501Y + Y505H	No change[c]

[a] The B.1.1.7, B.1.351, ~~and~~ B.1.617.2, and B.1.1.529/BA.1 variants were assessed using cell culture-expanded virus isolates and tested using a plaque reduction assay; the B.1.351, P.1, B.1.617.2, B.1.1.529/BA.1, and BA.1.1 variants ~~were as~~ assessed using cell culture-expanded isolates and tested using a microneutralization assay with a CPE-based endpoint titer to determine the $IC_{>99}$; the B.1.526/E484K and B.1.427/B.1.429/L452R substitutions were assessed using recombinant SARS-CoV-2 (USA/WA/1/2020 isolate with E484K or L452R) and tested using a plaque reduction assay.

[b] Key substitutions occurring in receptor binding domain of spike protein which are associated with each lineage.

[c] No change: <5-fold reduction in susceptibility when compared to ancestral control isolate using the same methodology.

[d] These viral variants have been tested with two different neutralization methodologies, both yielding <5-fold reductions in susceptibility.

[de] Isolates of the B.1.526 lineage harbor several spike protein amino acid substitutions, and not all isolates contain the E484K substitution (as of February 2021).

Regulatory Conclusion

Collectively, the revisions to the Fact Sheets detailed above do not alter the analysis of benefits and risks that underlies the initial authorization of EUA 111.

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/s/

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