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	May 18, 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

I. Information Regarding Available Alternatives for the EUA Authorized Use

Information regarding available alternatives to bebtelovimab is highlighted in Section 1 of the Fact Sheet for Health Care Providers. In order to provide consistency across EUA product fact sheets, the following information (in bold) has been added:

> Information Regarding Available Alternatives for the EUA Authorized Use
>
> Veklury (remdesivir) is FDA-approved for the treatment of 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, who are not hospitalized and have mild-to-moderate COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days
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> Although Veklury is an approved alternative 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, FDA does not consider Veklury to be an adequate alternative to bebtelovimab for this authorized use because it may not be feasible or practical for certain patients (e.g., it requires a 3-day treatment duration).
>
> **Other therapeutics are currently authorized for the same use as bebtelovimab. For additional information on all products authorized for treatment or prevention of COVID-19, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policyframework/emergency-use-authorization.**
>
> **For information on clinical studies of bebtelovimab and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov**

Similar wording was added to the Fact Sheet for Patients, Parents, and Caregivers.

II. Adverse Events with Bebtelovimab- Hypotension Events and Pregnancy Exposure Adverse Events

On April 21, 2022, FDA became aware of a list-serve posting regarding two events of hypotension associated with bebtelovimab infusion, including one in a pregnant woman. Upon further review by Division of Antivirals (DAV) and Division of Pharmacovigilance (DPV), it was noted that one of the two cases from the list-serve was also reported to FAERS. The Division of Antivirals subsequently requested that Eli Lilly submit a report from all available data sources of any other events of hypotension (in pregnant or not pregnant individuals) and any cases of adverse events in pregnant individuals, including events affecting mother or fetus.

Eli Lilly provided a summary of post-authorization and clinical trial hypotension exposure adverse events, as well as pregnancy adverse events (Table 1).

Table 1: Summary of Post-Authorization and Clinical Trial Hypotension and Pregnancy Exposure Adverse Events

Case Report Type / Patient Number	Treatment	Patient Age	Event Preferred Term	Event Outcomes	Post-Marketing or Clinical Trial
Hypotension					
US202204008839	Bebtelovimab	66	Chest discomfort; Dizzness; Feeling abnormal; Blood pressure decreased; Hyperhidrosis	Unknown	Post-Marketing
Hypotension and Pregnancy					
US202204006705	Bebtelovimab	30	Erythema; Dyspnea; Chest discomfort; Infusion related reaction; Maternal exposure during pregnancy	Recovered for all adverse events, except for maternal exposure which is unknown	Post-Marketing
Pregnancy					
US202108003050 (this case is linked to the same pregnancy as US202108003732)	Bamlanivimab, etesevimab, and bebtelovimab	31	Paternal exposure timing unspecified	Spontaneous abortion 1 month and 28 days following treatment	Clinical Trial
US202108003732 (this case is linked to the same pregnancy as US202108003050)	Bamlanivimab, etesevimab, and bebtelovimab	29	Abortion spontaneous; Maternal exposure timing unspecified	Spontaneous abortion 1 month and 28 days following treatment	Clinical Trial
US202204006107 (this case is linked to the same pregnancy as US202204008219)	Bebtelovimab	Fetus (35 weeks gestation)	Fetal heart rate decreased; Fetal exposure during pregnancy	Unknown	Post-Marketing
US202204008219 (this case is linked to the same pregnancy as US202204006107)	Bebtelovimab	27	Nausea; Vomiting; Infusion related reaction; Maternal exposure during pregnancy	Unknown	Post-Marketing

Review of Hypotension Adverse Events

The safety of bebtelovimab is primarily based on exposure of 602 ambulatory (non-hospitalized) subjects who received doses of bebtelovimab, alone or in combination with bamlanivimab and etesevimab, in the phase 1 and phase 2 portions of BLAZE-4, a randomized clinical trial. Two events of hypotension associated with a nonimmediate hypersensitivity event (i.e., after the first 24 hours of the infusion), were reported for individuals receiving bebtelovimab in combination with bamlanivimab and etesevimab.

As reported in Table 1, a post-authorization hypotension event was noted in a 66-year-old female patient. Medical history and concomitant medications were not provided. The patient received bebtelovimab via IV push and reported adverse events of chest discomfort/tightness, dizziness, feeling abnormal, hyperhidrosis, and a decrease in blood pressure. Signs and symptoms resolved after 10 minutes without any reported intervention. The patient was monitored for an additional hour and then discharged home. The event was not considered to be related to bebtelovimab by the reporter.

In addition to the events in Table 1, two additional cases were identified following review of the FAERS Public Dashboard. These cases were in a 72-year-old, who experienced hypotension, hypophagia, dehydration, and infusion-related reaction, and in a 43-year-old, who experienced infusion-related reaction, pallor, presyncope, hyperhidrosis, and dizziness.

Hypotension is listed as a possible symptom of infusion-related reaction under Section 5, Warnings and Precautions. At this time, DAV and DPV, as well as Eli Lilly, believe that the Fact Sheet for Health Care Providers adequately describes the risk of hypotension associated with infusion-related reactions following administration of bebtelovimab.

Review of Pregnancy Exposure Adverse Events

One pregnancy was reported during the clinical development program of bebtelovimab. A participant received bebtelovimab with bamlanivimab and etesevimab 25 days after her last menstrual period. She was subsequently determined to be pregnant by home testing; this was confirmed via blood sampling on Day 29. Approximately two months after monoclonal antibody infusion, the patient was reported to have had a spontaneous abortion at the gestational age of 8 weeks. No diagnostic tests were performed. The male partner of this individual also received bebtelovimab with bamlanivimab and etesevimab (see Table 1).

Since the EUA for bebtelovimab was granted on February 11, 2022, Lilly has received 3 spontaneously-reported cases of exposure to bebtelovimab during pregnancy. These 3 cases concerned 2 pregnancies and are also listed in Table 1.

A 27-year-old female received 175 mg bebtelovimab IV at 35 weeks gestation. Approximately 2 minutes after the infusion, the patient experienced a burning sensation throughout her chest and extremities, along with nausea and vomiting. The patient was tachycardic with a heart rate of 100-110 beats per minute, and blood pressure was 110/70. The patient received IV diphenhydramine, methylprednisolone, and famotidine. Bradycardia was noted in the fetus, with a heart rate of 50 beats per minute, for approximately 10 minutes. This prompted consideration of emergent Cesarian section but this was not executed as the fetal heart tracing recovered. For 15 minutes, there was transient rebound fetal tachycardia of 190 beats per minute with moderate variability. The participant was monitored for 4 hours and then discharged home. In another case, a 30-year-old female at 23 weeks gestation felt chest discomfort during infusion of bebtelovimab. The infusion was stopped but the participant subsequently experienced erythema of the face and chest and reported difficulty breathing. She received supplemental oxygen, methylprednisolone, diphenhydramine, and ondansetron, as well as 500 mL normal saline. Her symptoms subsequently resolved.

Lilly has requested outcomes information for both pregnancies; however, at this time these data are not yet available.

Review of the FAERS Public Dashboard revealed an additional case of a 38-year-old pregnant female who experienced flushing, maternal drugs affecting fetus, maternal exposure timing unspecified, headache, and back pain following bebtelovimab exposure.

DAV and DPV have evaluated this information, as well as other adverse event data from pregnant individuals who received other SARS-CoV-2 monoclonal antibody products and believe that the Fact Sheet for Health Care Providers, specifically Section 8.1, should be amended. The following bolded language has been added:

Severe hypersensitivity reactions and infusion-related reactions, have been observed with administration of bebtelovimab, including in pregnant patients [see Warnings and Precautions (5.1)]. There are risks to the mother and fetus associated with untreated COVID-19 in pregnancy as well as potential risks to the fetus associated with severe maternal hypersensitivity and infusion-related reactions (see Clinical Considerations).

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. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy (see Clinical Considerations).

Data
Nonclinical reproductive toxicity studies have not been performed with bebtelovimab. In tissue cross reactivity studies using human fetal tissues, no binding of clinical concern was detected for bebtelovimab. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, bebtelovimab has the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of bebtelovimab provides any treatment benefit or risk to the developing fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations
Disease-associated maternal and/or embryo-fetal risk
COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Maternal Adverse Reactions
Pregnant patients who develop severe hypersensitivity and infusion-related reactions should be managed appropriately, including obstetrical care *[see Warnings and Precautions (5.1)].*

For consistency, this language will be added to the Fact Sheets of other authorized monoclonal antibody products if their respective authorizations are updated based on currently circulating SARS-CoV-2 variants. Currently, bebtelovimab is the only monoclonal antibody authorized in all U.S. regions.

In order to further communicate this potential risk, the following bolded language has been added to the Fact Sheet for Patients, Parents, and Caregivers: “Severe allergic reactions have been observed with administration of bebtelovimab, including in pregnant patients.”

III. Pharmacokinetics

Lilly has provided an update to Table 1, entitled “Pharmacokinetic Parameters of Bebtelovimab Administered IV in Adults and Pediatric Patients (12 years of age and older weighing at least 40 kg)” in Section 12.3. These updates are based on the final PK parameters from Study PYAH and are bolded:

Table 1: Pharmacokinetic Parameters of Bebtelovimab Administered IV in Adults and Pediatric Patients (12 years of age and older weighing at least 40 kg)

	Bebtelovimab (175 mg) N=**585**
Systemic Exposure	
Geometric Mean (%CV) C_{max}, mcg/mL	59.**9 (31.9**)
Geometric Mean (%CV) $C_{day\ 29}$, mcg/mL	4.**55 (70.9)**
Geometric Mean (%CV) AUC_{inf}, mcg day/mL	**539 (41.5)**
Distribution	
Geometric Mean (%CV) Vss (L)	4.**55 (25.8)**
Elimination	
Geometric Mean (%CV) Elimination Half-Life (day)	11.5 **(27.0)**
Geometric Mean (%CV) Clearance (L/day)	0.**325 (41.5)**

Abbreviations: CV = coefficient of variation; C_{max} = maximum concentration; $C_{day,29}$ = drug concentration on day 29; AUC_{inf} = area under the concentration versus time curve from zero to infinity; Vss = steady-state volume of distribution.

IV. Microbiology

Antiviral resistance data within Section 12.4 was edited to provide updated information The edited portions are in bold:

Nonclinical selection studies using a directed evolution of a yeast displayed Spike RBD identified that substitutions at residues K444, V445, G446, and P499 interfered with bebtelovimab's ability to block the Spike RBD:ACE-2 interaction. Pseudotyped virus-like particle (VLP) neutralization assays confirmed a 5-fold or greater reduction in susceptibility to bebtelovimab of viral variants with the following substitutions: **K444E (>862),** K444N (>1,901-fold), K444Q (208-fold), K444T (>1,814-fold), V445A (111-fold), V445F (369-fold), V445G (>730-fold), G446D (69-fold), G446R (7-fold), G446V (8-fold), P499H (>1,606-fold), P499R (>1,870-fold), and P499S (25-fold). In the context of Delta spike protein, G446V substitution had reduced susceptibility of 16.4-fold.

Pseudotyped VLP assessment using the full-length spike genes from different variant lineages indicate that bebtelovimab retains activity (<5-fold reduction) against the Alpha (B.1.1.7, UK origin), Beta (B.1.351, South Africa origin), Gamma (P.1, Brazil origin), Delta (B.1.617.2, India origin), Delta [+K417N] (AY.1/AY.2, India origin), Epsilon (B.1.427/B.1.429, California origin), Iota (B.1.526, New York origin), Kappa (B.1.617.1, India origin), Lambda (C.37, Peru origin), Omicron (B.1.1.529/BA.1, South Africa origin), Omicron [+R346K] (BA.1.1), Omicron BA.2, **and Omicron BA.2.12.1 (BA.2 full-length spike + L452Q substitution) variant lineages** (Table 2). The Mu (B.1.621, Colombia origin) variant showed a reduction in susceptibility to bebtelovimab of 5.3-fold.

Table 2: Bebtelovimab Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Spike Protein Variants

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested[a]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	No change[b]
B.1.351	South Africa	Beta	K417N + E484K + N501Y	No change[b]
P.1	Brazil	Gamma	K417T + E484K + N501Y	No change[b]
B.1.617.2/AY.3	India	Delta	L452R + T478K	No change[b]
AY.1/AY.2 (B.1.617.2 sublineages)	India	Delta [+K417N]	L452R + T478K + K417N	No change[b]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	No change[b]
B.1.526[c]	USA (New York)	Iota	E484K	No change[b]
B.1.617.1	India	Kappa	L452R + E484Q	No change[b]
C.37	Peru	Lambda	L452Q + F490S	No change[b]
B.1.621	Colombia	Mu	R346K + E484K + N501Y	5.3
B.1.1.529/BA.1	South Africa	Omicron [BA.1]	G339D + S371L + S373P + S375F + K417N + N440K + G446S + S477N + T478K + E484A + Q493R + G496S + Q498R + N501Y + Y505H	No change[b]
BA.1.1	South Africa	Omicron [+R346K]	**BA.1 + R346K**	No change[b]
BA.2	South Africa	Omicron [BA.2]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N + N440K + S477N + T478K + E484A + Q493R + Q498R + N501Y + Y505H	No change[b]
BA.2.12.1	**USA**	**Omicron [BA.2+L452Q]**	**BA.2 + L452Q**	**No change[b]**

[a] Key substitutions occurring in the receptor binding domain of spike protein are listed. Pseudotyped VLP contained the full-length spike protein reflective of the consensus sequence for each of the variant lineages **with the exception of BA.2.12.1 which was a BA.2 full-length spike with L452Q substitution.**

[b] No change: <5-fold reduction in susceptibility.

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

In authentic SARS-CoV-2 assays, bebtelovimab retained activity (<5-fold reduction) against variant virus isolates from the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2/AY.3), Omicron (B.1.1.529/BA.1), Omicron [+R346K] (BA.1.1), **and Omicron [BA.2] lineages**, as well as SARS-CoV-2 (USA/WA/1/2020 isolate) engineered to express the L452R

substitution present in the Epsilon (B.1.427/B.1.429) lineage or the E484K substitution present in the Iota (B.1.526) lineage (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[e]	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]	**BA.1 + R346K**	No change[c]
BA.2	**South Africa**	**Omicron [BA.2]**	**G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N + N440K + S477N + T478K + E484A + Q493R + Q498R + N501Y + Y505H**	**No change[c,d]**

[a] The B.1.1.7, B.1.351, B.1.617.2, B.1.1.529/BA.1, and **BA.2** 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, BA.1.1, and **BA.2** variants were 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 sp ke 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 suscept bility.

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

Genotypic analysis and phenotypic testing are ongoing to monitor for potential bebtelovimab-resistance-associated spike variations in clinical trials. Baseline sequencing data are available for 611 of the subjects in the BLAZE-4 (Arms 9-14) Study. Of these, **552 (90.3%)** were infected with a variant of interest or concern, as designated by the WHO. No subject was infected with virus of the Omicron lineage or sub-lineages. The majority of subjects in the trial were infected with **Delta (49.9%)** and Alpha (28.6%). These were distributed across the treatment groups with Delta and Alpha infection rates of 60.2% and 23.1% in placebo, 31.3% and 41.8% in bebtelovimab alone arms, and 58.3% and 21.9% in the bebtelovimab with bamlanivimab and etesevimab arms, respectively. Gamma and Mu infections comprised 5.6% and 3.8% of the total infections respectively. Subjects infected with Beta, Delta [+K417N], Iota, and Lambda variants were the

minority with 0.5%, 0.8%, 0.7%, and 0.5% total infections, respectively. All other subjects in the trial had SARS-CoV-2 infections from either non-WHO classified viruses **(3.3%),** or the lineage was not able to be determined based on the baseline sequence data **(6.4%).** Detection of viral variants with a 5-fold or greater reduction in susceptibility to bebtelovimab at baseline has been rare, with only one G446V substitution (8-fold shift) observed transiently out of 611 subjects in the BLAZE-4 (Arms 9-14) study that had baseline sequencing available (0.2%, 1/611).

Analysis of treatment-emergent variants focused on changes at amino acid positions with known phenotypically confirmed bebtelovimab-associated variations (i.e., K444, V445, G446, and P499) in serial viral samples obtained in the BLAZE-4 (Arms 9-14) bebtelovimab Phase 2 Study. Treatment-emergent substitutions detected at ≥15% or ≥50% allele fractions at these positions included K444E/N, V445G, G446V, and P499H/R. These substitutions resulted in a 5-fold or greater reduction in susceptibility to bebtelovimab in pseudotyped VLP assays: **K444E (>862),** K444N (>1,901-fold), V445G (>730-fold), G446V (8-fold), P499H (>1,606-fold), and P499R (>1,870-fold). Additional treatment-emergent substitutions detected at ≥15% or >50% allele fractions outside the epitope in at least 2 subjects included C379F (n=2) and G404C (n=2), seen in bebtelovimab in combination with bamlanivimab and etesevimab arms.

Considering all substitutions detected at ≥15% allele fraction at positions K444, V445, G446, and P499, **5.5% (11/199)** of subjects treated with bebtelovimab alone harbored a variant that was treatment-emergent. This was more frequent than observed in the placebo arm (0%, 0/112), or when bebtelovimab was administered together with bamlanivimab and etesevimab (0.3%, 1/312). The appearance of these treatment-emergent bebtelovimab resistance-associated substitutions was associated with higher viral loads in the subjects in whom they were detected, but none of these subjects were hospitalized. The majority of the variants were first detected on Day 5 (n=3) and Day 7 (n=6) following treatment initiation.

Regulatory Conclusion:

Changes have been made to the Fact Sheet for Health Care Providers, as well as to the Fact Sheet for Patients, Parents, and Caregivers, in order to highlight the possibility of severe hypersensitivity and infusion-related reactions in pregnant individuals and potential associated risks to the fetus. Changes have also been made to the Fact Sheet for Health Care Providers, as well as to the Fact Sheet for Patients, Parents, and Caregivers, regarding other treatment options for consistency across authorized products. In addition, updates have been added to section 12 of the Fact Sheet for Health Care Providers. The analysis of benefits and risks that underlies the authorization of EUA 94 remains unchanged.

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