Emergency Use Authorization (EUA) for bamlanivimab 700mg IV

Center for Drug Evaluation and Research (CDER) Memorandum on Fact Sheet Update

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)[1]	90
Date of Memorandum	January 25, 2021
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)
Integrated Review Completion Date	November 9, 2020
Proprietary Name	n/a
Established Name/Other names used during development	bamlanivimab (LY3819253, LY-CoV555)
Dosage Forms/Strengths	700 mg IV
Therapeutic Class	SARS-CoV-2 spike protein directed human IgG1κ monoclonal antibody (mAb)
Intended Use or Need for EUA	mild to moderate COVID-19
Intended Population(s)	treatment of mild to moderate COVID-19 illness in adults and pediatric patients with positive results of direct SARS-

[1] If a Pre-EUA is in existence at the time of the EUA request submission and has been assigned an EUA number, the EUA request should use the same EUA number and electronic archive file.

	CoV-2 viral testing who are 12 years of age and older, who weigh at least 40 kg, and who are at high risk for progressing to severe COVID-19 illness and/or hospitalization

I. Issue Summary

The current Emergency Use Authorization (EUA) 90 authorized use for bamlanivimab 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 for progressing to severe COVID-19 and/or hospitalization. This memorandum provides a brief summary of the proposed changes to the Health Care Provider Fact Sheets and Patient Fact Sheets for EUA 90 for bamlanivimab. The following are the most recent major changes made to the version authorized on December 11, 2020.

RECENT MAJOR CHANGES SINCE 11-Dec-2020

- Dose Preparation and Administration Instructions (Section 2.4) - provides updated minimum infusion times based on size of infusion bag used
- Warning: Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions (Section 5.1) - addition of new symptoms
- Warning: Clinical Worsening After Bamlanivimab Administration (Section 5.2) – new warning

Rationale for changes to the Dose Preparation and Administration Instructions (Section 2.4)

The December 11, 2020 update streamlined the preparation instructions to remove the need to withdraw 20 mL of 0.9% normal saline infusion solution from a prefilled 250mL bag prior to then injecting the bamlanivimab 20 mL dose (700mg/20mL) into the infusion bag; instead, the dose of bamlanivimab 20 mL could now be injected directly into the prefilled 250 mL bag and administered over 60 minutes. Subsequently, Lilly proposed further streamlining the preparation and administration instructions in order to respond to stakeholders requests for additional flexibility in preparation and administration with the goals of improving efficiency of administration to high-risk outpatients infected with COVID-19, allowing shorter infusion times and improving uptake of drug utilization during this current pandemic surge of COVID-19 in the US. However, the dosage of bamlanivimab 700 mg has not changed since the original authorization of November 9, 2020 only the preparation and administration instructions. Based on the above Lilly provided the following:

- Compatibility data that covers the range of concentrations that results from use of various 0.9% normal saline diluent volumes including 50 mL, 100 mL, 150 mL and 250 mL. These are standard prefilled diluent bags at volumes readily available for clinical use. A range of volumes are included to broaden flexibility and to address shortages of a particular prefilled volume bag and to provide other options for use. Additionally, the

smaller volumes allow for shorter infusion times, thus, decreasing burden both on patients and the health care system.

- Data to justify that sufficient head space is available for the range of prefilled 0.9% normal saline infusion bags sizes to accommodate the direct addition of 20mL of bamlanivimab into the pre-filled bag and to allow for adequate mixing. Additionally, Lilly provided information demonstrating that no leaks occurred after inclusion of the extra 20 mL with manipulation of the bag under typical use. Data was also included for a variety of standard prefilled 0.9% normal saline bags from different commonly used vendors (e.g. (b) (4))

OBP reviewed these compatibility data and real use data and determined they were sufficient to allow for updates to the preparation and administration instructions. By including the lower volume for diluent, the minimum infusion times were updated and now range from 16 minutes to 60 minutes with a consistent maximum infusion rate of 270 mL/hr regardless of the size of infusion bag used. Details of the changes are below in Section II of this memorandum.

Rationale for Changes to the Warning Sections – Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions and Addition of Warning for Clinical Worsening After Bamlanivimab Administration

As part of Emergency Use Authorization for bamlanivimab, health care providers must submit reports all medication errors and serious adverse events potentially related to bamlanivimab. These data were reviewed by DAV and the Division of Pharmacovigilence (DPV). Following review of 518 cases submitted to the FAERS database, revisions were made to the Health Care Provider Fact Sheet for bamlanivimab to more accurately reflect the available safety information. Specifically, new signs and symptoms were added to Section 5.1 (Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions) and Section 5.2 (Clinical Worsening After Bamlanivimab Administration) was added. Modifications consistent with these changes were also added to the Patient Fact Sheet. See section II below for details.

II. Summary of Revision to EUA Fact Sheets

Dose Preparation and Administration Instructions (Section 2.4) –

- provides updated minimum infusion times based on size of infusion bag used
- minor updates to clarify preparation instructions to align with updates in Table 1 as included below

Table 1: Recommended Dilution and Administration Instructions for Bamlanivimab[a]

Drug: Add 20 mL of bamlanivimab (1 vial) to a prefilled infusion bag and administer as instructed below		
Size of prefilled 0.9% Sodium Chloride infusion bag	**Maximum Infusion Rate**	**Minimum Infusion Time**
50 mL	270 mL/hr	16 minutes
100 mL	270 mL/hr	27 minutes
150 mL	270 mL/hr	38 minutes
250 mL	270 mL/hr	60 minutes

[a] 700 mg of bamlanivimab (20 mL) is added to an infusion bag and administered as a single intravenous infusion.

Warning: Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions (Section 5.1) –

- Based on review of the 518 cases submitted to the FAERS database, new symptoms that were more frequently reported and not included in the prior authorized fact sheet was added to the list as highlighted below in bolded font

Signs and symptoms of infusion-related reactions may include:

- fever, **difficulty breathing, reduced oxygen saturation,** chills, **fatigue, arrythmia (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, dizziness, and **diaphoresis**.
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Warning: Clinical Worsening After Bamlanivimab Administration (Section 5.2)

- Based on review of cases with reports of clinical worsening after administration of bamlanivimab, DAV and DPV agreed that a new section should be added to the warning to make HCPs aware that clinical worsening after treatment has been reported and could occur. However, many of the cases were confounded due to underlying morbidities, age or other factors and it is challenging to determine if the clinical worsening was a result of administration of bamlanivimab or due to progression of COVID-19.
- The following is added to Section 5.2:
  - Clinical worsening after administration of bamlanivimab has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrythmia (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 use or were due to progression of COVID-19.

Changes to Patient Fact Sheet

- Changes consistent with the reviewed safety data were updated to the Patient Fact Sheet. Specifically, the symptom list was expanded to include the same information as in the HCP Fact Sheet and new information regarding clinical worsening was added under “What are the important possible side effects of bamlanivimab?”.

What are the important possible side effects of bamlanivimab?

Possible side effects of bamlanivimab are:

- Allergic reactions. Allergic reactions can happen during and after infusion with bamlanivimab. Tell your healthcare provider right away if you get any of the following signs and symptoms of allergic reactions: fever, chills, nausea, headache, shortness of breath, low **or high blood pressure, rapid or slow heart rate, chest discomfort or pain, weakness, confusion**, **feeling tired,** wheezing, swelling of your lips, face, or throat, rash including hives, itching, muscle aches, dizziness, and **sweating**. These reactions may be severe or life threatening.

- **Worsening symptoms after bamlanivimab: You may experience new or worsening symptoms after infusion, including fever, difficulty breathing, rapid or slow heart rate, tiredness, weakness or confusion. If these occur, contact your healthcare provider or seek immediate medical attention as some of these events have required hospitalization. It is unknown if these events are related to bamlanivimab infusion or are due to the progression of COVID-1**

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.

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/s/

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