Drug Monograph

Drug Name: **Etesevimab Vial**
Drug Class: **Monoclonal Antibodies (mAbs) Against SARS-CoV-2**
Prepared For: MO HealthNet
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☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Etesevimab is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution available as injection 700 mg/20 mL (35 mg/mL) in a single-dose vial for intravenous infusion
Manufacturer:	Manufactured by: Eli Lilly and Company, Indianapolis, IN 46285, USA.
Summary of Findings:	The efficacy of bamlanivimab and etesevimab was based on a randomized, double-blind, placebo-controlled Phase 2/3 trial in outpatients with mild to moderate COVID-19. Patients were randomized to receive a single IV infusion of bamlanivimab 2,800 mg and etesevimab 2,800 mg or placebo. Significant improvement in endpoints of reduced viral load, accelerated symptom resolution, and 70% risk reduction in rate of hospitalization and deaths were noted in the trial. Blaze 4 trial initial results demonstrated that bamlanivimab 700 mg and etesevimab 1,400 mg are similar to bamlanivimab 2,800 mg and etesevimab 2,800 mg in viral load change from baseline.

Status Recommendation:	☐ Clinical Edit ☒ Open Access	☐ PA Required ☐ PDL
Type of PA Criteria:	☐ Appropriate Indications ☒ No PA Required	☐ Non-Preferred ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2,3]

The coronavirus disease 2019 (COVID-19) that has caused a global pandemic was the result of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The primary route of transmission of SARS-CoV-2 is direct person to person via respiratory particles. Reactions to COVID-19 range from asymptomatic to acute respiratory distress syndrome (ARDS) and multiorgan dysfunction. For non-severe COVID-19 infections in patients with certain risk factors for severe disease, antibody-based therapies have demonstrated possible benefits. There have been over 150 million confirmed cases of COVID-19 reported worldwide.

Dosage Form [4]

Etesevimab is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution available as injection 700 mg/20 mL (35 mg/mL) in a single-dose vial for intravenous infusion.

Manufacturer [4]

Manufactured by: Eli Lilly and Company, Indianapolis, IN 46285, USA.

Indication(s) [4]

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved products bamlanivimab and etesevimab administered together 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 SARSCoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. LIMITATIONS OF AUTHORIZED USE: Bamlanivimab and etesevimab are not authorized for use in patients: who are hospitalized due to COVID-19, or who require oxygen therapy due to COVID-19 or who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity. Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Clinical Efficacy [4,5] (mechanism of action/pharmacology, comparative efficacy)

Etesevimab is a recombinant neutralizing human IgG1κ mAb to the spike protein of SARS-CoV-2, with amino acid substitutions in the Fc region (L234A, L235A) to reduce effector function.

Etesevimab binds the spike protein with a dissociation constant K_D = 6.45 nM and blocks spike protein attachment to the human ACE2 receptor with an IC_{50} value of 0.32 nM (0.046 µg/mL).

Pharmacokinetics:

C_{max}	504 µg/mL (90% CI: 262 to 974 µg/mL) following approximately 1 hour 1400mg IV infusion
Volume of Distribution	2.38L and 1.98L (central and peripheral compartments, respectively)
Metabolism	Expected to be degraded into small peptides and component amino acids via catabolic pathways in the same manner as endogenous IgG antibodies
Clearance (CL)	0.128 L/hr
Terminal Half-life	25.1 days

Clinical Trials Experience: Mild to Moderate COVID-19

STUDY 1 DESIGN (BLAZE-1)	Randomized, double-blind, placebo-controlled Phase 2, clinical trial studying bamlanivimab and etesevimab (n=577)
INCLUSION CRITERIA	• Ambulatory adult subjects who were not hospitalized and had at least 1 or more COVID-19 symptoms that were at least mild in severity.
EXCLUSION CRITERIA	• Not meeting inclusion criteria
TREATMENT REGIMEN	Treatment was initiated within 3 days of obtaining the clinical sample for the first positive SARS-CoV-2 viral infection determination. Subjects were treated with a single infusion of: • Bamlanivimab 2,800 mg and etesevimab 2,800 mg (N=112) • Bamlanivimab alone (at doses of 700 mg [N=101], 2,800 mg [N=107], or 7,000 mg [N=101]) • Placebo (N=156)
RESULTS	The pre-specified primary endpoint in this Phase 2 trial was the change in viral load from baseline to Day 11 for 2,800 mg bamlanivimab and 2,800 mg etesevimab-treated subjects versus placebo. The data are from an interim analysis after all enrolled subjects completed at least Day 29 of the trial. Most subjects, including those receiving placebo, effectively cleared virus by Day 11 (Figure 1).

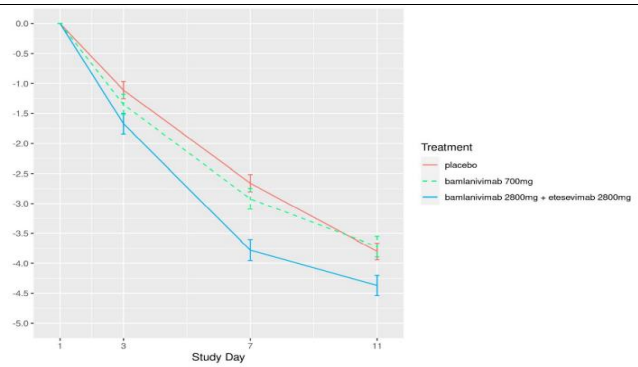

Figure 1: SARS-CoV-2 Viral Load Change from Baseline by Visit from the Phase 2 Portion of BLAZE-1.

The predefined secondary endpoint of the study was the COVID-19-related hospitalizations or emergency room visits within 28 days after treatment.

A lower proportion of bamlanivimab and etesevimab-treated subjects progressed to COVID-19-related hospitalization or emergency room visits compared to placebo-treated subjects. No deaths occurred in any treatment group.

Proportion of Subjects with Events of Hospitalization or Emergency Room Visits within 28 Days After Treatment

Treatment	N[a]	Events	Proportion of Subjects (%)
Placebo	156	9	6
Bamlanivimab and etesevimab[b]	122	1	1
Bamlanivimab[c] 700 mg	101	1	1

[a] N=number of treated patients in analysis
[b] The doses were bamlanivimab 2,800 mg and etesevimab 2,800mg.
[c] Results for other doses of bamlanivimab were suggestive of a flat dose-response relationship for this endpoint.

The absolute risk reduction for bamlanivimab and etesevimab-treated subjects compared to placebo is greater in subjects at higher risk of hospitalization according to the high risk criteria.

Proportion of Subjects with Events of Hospitalization or Emergency Room Visits for Subjects at Higher Risk of Hospitalization

Treatment	N[a]	Events	Proportion of Subjects (%)
Placebo	68	7	10
Bamlanivimab and etesevimab[b]	38	1	3
Bamlanivimab[c] 700 mg	46	1	2

[a] N=number of treated patients in analysis
[b] The doses were bamlanivimab 2,800 mg and etesevimab 2,800mg.
[c] Results for other doses of bamlanivimab were suggestive of a flat dose-response relationship for this endpoint.

SAFETY	Discussed in the Adverse Effects section below.

Clinical Trials Experience: Mild to Moderate COVID-19

STUDY 1 DESIGN (BLAZE-1)	Randomized, double-blind, placebo-controlled, Phase 3, clinical trial studying bamlanivimab and etesevimab (n=1,035)

INCLUSION CRITERIA	• Patients enrolled in these dose arms met the criteria for high-risk. High risk is defined as patients who meet at least one of the following criteria:
	  ○ Body mass index (BMI) ≥35,
	  ○ Chronic kidney disease,
	  ○ Diabetes,
	  ○ Immunosuppressive disease,
	  ○ Currently receiving immunosuppressive treatment,
	  ○ ≥65 years of age;
	  ○ ≥55 years of age AND have:
	  ▪ Cardiovascular disease, or
	  ▪ Hypertension, or
	  ▪ Chronic obstructive pulmonary disease/other chronic respiratory disease
	• Are 12 – 17 years of age AND satisfy at least one of the following at the time of screening:
	  ○ Are pregnant
	  ○ Have a BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm
	  ○ Have sickle cell disease
	  ○ Have congenital or acquired heart disease
	  ○ Have neurodevelopmental disorders, for example, cerebral palsy
	  ○ Have a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)
	  ○ Have asthma, reactive airway or other chronic respiratory disease that requires daily medication for control
	  ○ Have type 1 or type 2 diabetes
	  ○ Have chronic kidney disease
	  ○ Have immunosuppressive disease
	  ○ Are currently receiving immunosuppressive treatment

EXCLUSION CRITERIA	• Not meeting inclusion criteria
TREATMENT REGIMEN	A single infusion of bamlanivimab 2,800 mg and etesevimab 2,800 mg (N=518) or placebo (N=517).
RESULTS	The primary endpoint was the proportion of subjects with COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause by Day 29. Events occurred in 36 subjects treated with placebo (7%) as compared to 11 events in subjects treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together (2%) [p<0.001], 70% reduction. Deaths: no deaths in treatment group, 10 deaths in placebo group

	Secondary endpoints include mean change in viral load from baseline to Day 3, 5, and 7. At Day 7, 29% of subjects treated with placebo and 10% of subjects treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together had persistently high viral loads (p< 0.000001), which was defined as SARS-CoV-2 viral load>5.27.
SAFETY	Discussed in the Adverse Effects section below.

Clinical Trials Experience: Mild to Moderate COVID-19

STUDY 1 DESIGN (BLAZE-4)	Ongoing Phase 2, randomized, double-blind, placebo-controlled with bamlanivimab and etesevimab (n=515)
INCLUSION CRITERIA	• 18 to 64 years old • Not hospitalized and had at least 1 or more COVID-19 symptoms that were at least mild in severity
EXCLUSION CRITERIA	• Subjects ≥65 years old • BMI ≥35
TREATMENT REGIMEN	Treatment was initiated within 3 days of obtaining the clinical sample for the first positive SARS-CoV-2 viral infection determination. Subjects were treated with a single infusion of: • Bamlanivimab 700 mg and etesevimab 1,400 mg (N=158) • Bamlanivimab 2,800 mg and etesevimab 2,800 mg (N=101) • Bamlanivimab alone at a dose of 700 mg (N=103) • Placebo (N=153)
RESULTS	The pre-specified primary endpoint in this Phase 2 trial was the proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (+2 days). The rates were 31% (42/135) for placebo, 14% (21/147, p <0.001 versus placebo) for bamlanivimab 700 mg and etesevimab 1,400 mg together, and 10% (10/99, p<0.001 versus placebo) for bamlanivimab 2,800 mg and etesevimab 2,800 mg together.

Contraindications [(4)]

- None

Warnings and Precautions [(4)]

- There is limited clinical data available for etesevimab. Serious and unexpected adverse events may occur that have not been previously reported with use of bamlanivimab and etesevimab together.
- Pregnancy: Insufficient data to evaluate
- Lactation: No available data

Adverse Effects [3]

Phase 2 Data from BLAZE-1

Most common, ≥ 1 %	bamlanivimab and etesevimab (n =112) %	Placebo(n =156) %
Nausea	4	4
Pruritus	2	1
Pyrexia	1	0

Phase 3 Data from BLAZE-1

Most common, ≥ 1%	bamlanivimab and etesevimab (n =518) %	Placebo(n =517) %
Nausea	1	1
Dizziness	1	1
Rash	1	1

Drug Interactions [4]

Etesevimab is not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

Dosage and Administration [4]

The dosage etesevimab 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) is etesevimab 1,400 mg. Administer bamlanivimab and etesevimab together as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset. Under this EUA, bamlanivimab and etesevimab must be diluted and administered together as a single intravenous infusion.

Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion[a] in Patients Weighing 50 kg or More

Drug[a]: Add 20 ml of bamlanivimab (1 vial) and 40 ml of etesevimab (2 vials) for a total of 60 ml 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	310 ml/hr	21 minutes
100 ml	310 ml/hr	31 minutes
150 ml	310 ml/hr	41 minutes
250 ml	310 ml/hr	60 minutes

[a] 700 mg of bamlanivimab and 1,400 mg of etesevimab are added to the same infusion bag and administered together as a single intravenous infusion

Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion[a] in Patients Weighing Less Than 50 kg

Drug[a]: Add 20 ml of bamlanivimab (1 vial) and 40 ml of etesevimab (2 vials) for a total of 60 ml 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	310 ml/hr	21 minutes
100 ml	310 ml/hr	31 minutes
150 ml	310 ml/hr	41 minutes
250 ml[b]	266 ml/hr	70 minutes

[a] 700 mg of bamlanivimab and 1,400 mg of etesevimab are added to the same infusion bag and administered together as a single intravenous infusion

[b] The minimum infusion time for patients weighing less than 50 kg who are administered bamlanivimab and etesevimab together using the 250 ml prefilled 0.9% Sodium Chloride infusion bag must be extended to at least 70 minutes to ensure safe use (endotoxin load).

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/Month
Etesevimab		Eli Lilly and Co.	1,400 mg (2 vials of 700 mg/20 ml)	$0

** Wholesale Acquisition Cost

Conclusion (1-5)

Bamlanivimab and etesevimab has been authorized for emergency use under an Emergency Use Authorization (EUA) by The U.S. Food and Drug Administration (FDA). The efficacy of bamlanivimab and etesevimab was based on a Phase 2/3 trial in outpatients with mild to moderate COVID-19. Significant improvement in endpoints of reduced viral load, accelerated symptom resolution, and 70% risk reduction in rate of hospitalization and deaths were noted in the trial. Antibody-based therapies have shown potential benefits for patients with certain risk factors for severe disease. Our understanding of COVID-19 and how to manage the disease continues to grow.

Recommendation

MO HealthNet Division recommends Open Access status for this product.

References

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3) McIntosh, Kenneth. COVID-19: Epidemiology, virology, and prevention. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on May 12, 2021.)
4) Fact Sheet For Health Care Providers Emergency Use Authorization (Eua) Of Bamlanivimab And Etesevimab (fda.gov) https://www.fda.gov/media/145802/download
5) IPD Analytics Payer & Provider Insights_Rx Brief: Infectious Disease_COVID-19 Update: Recent Key Treatment Updates_02 16 2021.pdf

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