Treatment Plan for Mild to Moderate COVID-19 Using Bamlanivimab at CMH

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product bamlanivimab (LY-CoV555) 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) 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.

There is limited clinical data available for bamlanivimab. Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that bamlanivimab may be effective for the treatment of mild to moderate COVID-19 in patients as specified in the Fact Sheet for Health Care Providers – Emergency Use Authorization (EUA) of bamlanivimab.
This EUA for bamlanivimab will end when the Secretary of HHS determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

Purpose:
Define the criteria and provide guidance to providers for the use of bamlanivimab at CMH for the treatment of mild to moderate disease due to COVID-19 in patients who are at high risk for progressing to severe COVID-19 and/or hospitalization.

Background:
Bamlanivimab is a recombinant neutralizing human IgG1k monoclonal antibody to the spike protein of SARS-CoV-2. Bamlanivimab binds to the spike protein, blocking attachment of the human ACE2 receptor. It is an investigational drug and is not currently approved for any indication.

Approved Available Alternatives:
For patients who have mild to moderate COVID-19 who are at high risk for progressing to severe COVID-19 and/or hospitalization the only available alternative is the unapproved, investigational monoclonal antibody combination Casirivimab and Imdevimab. Casirivimab and Imdevimab use is authorized for emergency use by the FDA.
Additional information on COVID-19 treatments can be found at https://www.covid19treatmentguidelines.nih.gov/whats-new/ and https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs
The health care provider should visit https://clinicaltrials.gov/ to determine whether the patient may be eligible for enrollment in a clinical trial.

Inclusion/Exclusion Criteria:
A tiered approach to eligibility is being utilized by the Maine CDC to ensure supply is available for the most vulnerable populations:

- Criteria for tiering was established by a State collaborative of clinicians and the Maine CDC and based on available published data and EUA criteria
- The Active Tier will be reevaluated as supply/demand changes
- Long Term Care residents
    - Patients that are residents of long term care facilities are exempt from the Maine CDC collaborative tiering restrictions.
    - If a patient is a resident of a long term care facility AND meets the inclusion criteria AND any of the criteria in any of the tiers, they are eligible to receive the product.

Patient MUST meet inclusion criteria AND criteria for the Active Tier

Inclusion criteria:

- Age greater than or equal to 12
- Weight greater than or equal to 40 kg
- Not requiring hospitalization due to COVID-19
- Presents within 10 days of symptom onset (EUA)
    - Maine CDC collaborative has agreed on limiting use to within 5 days of symptom onset
- Confirmed COVID-19 via laboratory testing in previous 10 days (EUA) (should be given as soon as possible after a positive viral test for SARS-CoV-2)
    - Maine CDC collaborative has agreed on limiting use to within 5 days of confirmed test
- Mild to moderate symptoms not requiring supplemental oxygen (or not greater than baseline, if on baseline oxygen) due to COVID-19

If all Inclusion Criteria are met, review the patient's eligibility based on the Active Tier

- **Tier 1 (Any of the Following)**
    - Greater than or equal to 65 years old
    - 18 to 64 years old AND Body Mass Index (BMI) greater than or equal to 35
- **Tier 2 (Any of the Following)**
    - Any of Tier 1
    - 12 to 17 years old with BMI greater than 85th percentile for their age and gender based on the CDC growth charts https://www.cdc.gov/growthcharts/clinical_charts.htm
- **Tier 3 (Any of the Following)**
    - Any of Tier 1 and Tier 2 criteria
    - Chronic Kidney Disease
    - Diabetes Mellitus
    - Immunosuppressive disease or therapy
    - Greater than or equal to 55 years old AND one or more of following:
        - Cardiovascular Disease
        - Hypertension
        - COPD or Chronic respiratory illness
    - 12 to 17 years old AND one or more of following:

- BMI greater than 85th percentile for their age and gender based on the CDC growth charts https://www.cdc.gov/growthcharts/clinical_charts.htm
- Sickle Cell Disease
- Congenital or acquired heart disease
- Neurodevelopmental disorder (e.g. cerebral palsy)
- A medical-related technological dependence not related to COVID-19 (e.g. tracheostomy, chronic feeding tube, home vent support)
- Asthma or respiratory disease requiring daily medication

Hospitalized patients

- See exclusion Criteria
- Use may be considered in patients hospitalized for reasons **other than** COVID-19, so long as the terms and conditions of the EUA are met. Infectious disease consult required. If it is decided to use this medication in someone who is not hospitalized due to COVID-19 this reasoning must be clearly documented in the patient's EMR.

Exclusion criteria:

- Patients who are hospitalized due to COVID-19
  - Benefit of treatment with bamlanivimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.
- Patients who require oxygen therapy due to COVID-19
- Patients 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
- Not authorized for patients weighing less than 40 kg or those less than 12 years of age.
- Patients with known hypersensitivity to any ingredient of bamlanivimab must not receive bamlanivimab (Contains bamlanivimab, L-histidine, L-histidine hydrochloride monohydrate, sodium chloride, sucrose, polysorbate and water for injection).

Use with Caution in the Following Patients:

- Pregnancy: There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Bamlanivimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus. Nonclinical reproductive toxicity studies have not been performed with bamlanivimab. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, it has the potential to be transferred from the mother to the developing fetus. It is unknown if this transfer to the fetus provides any treatment benefit or risk to the fetus.
- Lactation: There are no available data on the presence of bamlanivimab in human or animal milk, the effects on breastfed infant, or the effects on milk production. Maternal IgG is known to

be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bamlanivimab and any potential adverse effects on the breastfed child from bamlanivimab or from underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

- Pediatric use: Safety and efficacy has not been assessed in pediatric patients. The recommended dosing regimen is expected to result in comparable serum exposures of bamlanivimab in patients 12 years of age and older weighting at least 40 kg as observed in adults based on pharmacokinetic modeling approach which accounted for effect of body weight changes associated with age on clearance and volume of distribution.
- Renal impairment: bamlanivimab is not eliminated intact in the urine, thus renal impairment is not expected to affect exposure
- Hepatic impairment: no dose adjustment in patients with mild hepatic impairment. Bamlanivimab has not been studied in patients with moderate or severe hepatic impairment

Dosing:

The dosage in adults and pediatric patients (12 years of age and older weighting at least 40 kg) is 700mg diluted and administered as a single IV infusion over at least 60 minutes. No dosage adjustment is recommended based on age, sex, race, body weight, renal or mild hepatic impairment, during pregnancy or while lactating, disease severity or for inflammation.

Administration:

- Prime the infusion set.
    - Polyvinyl chloride (PVC) or polyethylene (PE) lined PVC infusion set
- Use of an inline or add on 0.20/0.22 micron polyethersulfone (PES) filter is strongly recommended.
- Administer the entire infusion solution in the bag via pump or gravity over at least 60 minutes
- Once infusion is complete, flush the infusion line to ensure delivery of the required dose.

Potential Drug Interactions:

Bamlanivimab 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

Monitoring Parameters:

- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.
    - Monitor for infusion related reactions (e.g. fever, chills, hypotension, rash, pruritus) and hypersensitivity/anaphylaxis

- The following, at minimum, should be followed

Assessments	Pre-dose	On Treatment	Post-dose/Follow up
Vital Signs	X	X	X
Medical History	X		
Physical Exam	X		X
Monitor for Adverse Reactions/Events		X	X

- If the infusion must be discontinued due to an infusion reaction, discard any unused product.

Previously reported events:

- There are limited clinical data available. Serious and unexpected adverse events may occur that have not been previously reported with bamlanivimab use.
- Hypersensitivity including Anaphylaxis and Infusion-related reactions
    - There is the potential for serious hypersensitivity reaction, including anaphylaxis, with administration of bamlanivimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.
- Infusion-related reactions have been observed
    - Fever, chills, nauseas, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticarial, pruritus, myalgia, dizziness
    - If this occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.
- There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

Overdose:

- Doses up to 7000 mg have been administered in clinical trials without dose limiting toxicity. Treatment of overdose consists of general supportive measures.

Additional Physician Requirements:

- The prescribing healthcare provider and/or the provider's designee are/is responsible for mandatory reporting of all medication errors and serious adverse events potentially related to bamlanivimab treatment within 7 calendar days from the onset of the event
    - Completion of FDA MedWatch Form to report all medication errors and serious adverse events is mandatory. See *Reporting* Section for additional information on how to report.
    - In addition, a copy of all FDA MedWatch forms should be provided to Eli Lilly and Company
- The prescribing health care provider and/or designee is to provide mandatory responses to requests from FDA for information about adverse events and medication errors

- Healthcare provider must:
    - Obtain written consent
        - Scan into EMR copy of fully signed consent form
    - Communicate to the patient or parent/caregiver as age appropriate, information consistent with the "Fact Sheet for Patients, Parents and Caregivers" (and provide a copy of the Fact sheet) prior to the patient receiving bamlanivimab including:
        - FDA has authorized the emergency use of bamlanivimab for the treatment of mild to moderate 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 progressing to severe COVID-19 and/or hospitalization
        - The patient or parent/caregiver has the option to accept or refuse treatment
        - The significant known and potential risks and benefits of bamlanivimab and the extent to which such potential risks and benefits are unknown
        - Information on available alternative treatments and the risks and benefits of those alternatives, including clinical trials
        - Patients treated with bamlanivimab should continue to self-isolate and use infection control measures according to CDC guidelines.
    - Must document in the patients' medical record that the patient/caregiver has been:
        - Given the "Fact sheet for Patients, Parents and Caregivers"
        - Informed of alternatives to receiving authorized bamlanivimab and
        - Informed that bamlanivimab is an unapproved drug that is authorized for use under this Emergency Use Authorization
    - Provide patients that are discharged home post-infusion with follow up instructions in the event they experience adverse effects from treatment

Reporting:

- The healthcare provider/ designee is responsible for reporting of all medication errors and serious adverse events potentially attributable to bamlanivimab within 7 calendar days of the event.
- The reports should include unique identifiers and the words "Bamlanivimab treatment under Emergency Use Authorization (EUA)" in the description section of the report
- The healthcare provider/ designee is responsible for providing mandatory responses to requests from the FDA for information about adverse events and medication errors.

Health care providers/ designee must submit a report on all of the following

What to Report	When to Report / To Whom	When to Report / To Whom
Medication errors	Within 48 hours of onset of the event to the Clinical Research Department	Within 7 calendar days from onset of the event to FDA and Eli Lilly and Company
Unexpected Adverse Events occurring during bamlanivimab treatment (for example, diagnoses or findings that change the clinical care of the patient)	Within 48 hours of onset of the event to the Clinical Research Department	Within 7 calendar days from onset of the event to FDA and Eli Lilly and Company
Serious Adverse Events related to/potentially attributable to bamlanivimab	Within 48 hours of onset of the event to the Clinical Research Department	Within 7 calendar days from onset of the event to FDA and Eli Lilly and Company
Deaths	Within 48 hours of onset of the event to the Clinical Research Department	Within 7 calendar days from onset of the event to FDA and Eli Lilly and Company

Serious Adverse Events are defined as:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- A medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly

Reports must be submitted to the FDA and Eli Lilly and Company. The Clinical Research Department can aid in this process.

(1) Email all of the following Clinical Research Department staff:
- Dr. Kathryn Rohr rohrka@cmhc.org
- Kylie Guy guyky@cmhc.org
- Serena Crowley crowlese1@cmhc.org
- Jennifer Chase chaseje@cmhc.org

(2) Submit adverse event reports to FDA MedWatch using one of the following methods:
- Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
- By using a postage-paid Form FDA 3500 (available at https://www.fda.gov/media/76299/download) and returning by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), or by fax (1-800-FDA-0178), or

- Call 1-800-FDA-1088 to request a reporting form
- Submitted reports should include in the field name, “Describe Event, Problem, or Product Use/Medication Error” a statement “Bamlanivimab treatment under Emergency Use Authorization (EUA).”

(3) Submit a copy of all FDA MedWatch forms to Eli Lilly and Company, Global Patient Safety

- Fax: 1-317-277-0853
- E-mail: mailindata_gsmtindy@lilly.com
- Call: 1-855-5455921

References:

Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Bamlanivimab accessed 1.6.21