(Draft: updated after HTAC Meeting on 6th October 2021)

Protocol for Using Bamlanivimab+Etesevimab Anti-SARS-CoV-2 Monoclonal Antibodies

The Bamlanivimab+Etesevimab are anti-SARS-CoV-2 monoclonal antibodies which have received EUA (Emergency Use Authorization) from US FDA as well as conditional use approval from the MoHP, Department of Drug Administration (DDA) in Nepal.

Recommended Use (Eligibility Criteria):

The anti-SARS CoV-2 monoclonal antibodies combination of Bamlanivimab and Etesevimab should be used for treatment of high-risk patients as noted below (See "B") to prevent progression of COVID-19 at an early stage of infection (less than 7 days).

To be eligible for treatment with these monoclonal antibodies, patients must meet criteria "A", "B", and at least one criteria from "C" below:

A. Adults over 18 years with positive SARS-CoV-2 PCR.

B. Early stage of infection: within first 7 days of onset of symptoms

C. The patients who are at high-risk of clinical progression include the patients with following conditions:

1. Older age, over 65 years
2. Obesity (adults with BMI >25 kg/m^2)
3. Pregnancy
4. Chronic kidney disease
5. Diabetes mellitus
6. Immunosuppressive disease or immunosuppressive treatment
7. Cardiovascular disease, including coronary artery disease, cardiomyopathies, and CHF
8. Chronic lung diseases (e.g., COPD, moderate to severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension)
9. Sickle cell disease
10. Neurodevelopmental disorders (e.g., cerebral palsy)
11. other conditions that confer medical complexity (e.g., genetic or metabolic syndromes, severe congenital anomalies)
12. Medical-related technological dependence (e.g., tracheostomy, gastrostomy, or on ventilation)

Not recommended in the following clinical scenarios (Exclusion Criteria):

1. Patients who are severely ill secondary to COVID-19 requiring hospitalization (may cause more harm)
2. Patients who require oxygen therapy or increase in oxygen flow rate secondary to COVID-19
3. Patients exposed to or infected with variants with known to be resistant

e.g., Gamma (P.1) and Beta (B.1.351) have reduced susceptibility to both bamlanivimab and etesevimab; [this combination remains active against the Delta variant (B.1.617.2)]

4. Pre-exposure prophylaxis for prevention of COVID-19

Dosing Recommendations for adults:

- Bamlanivimab/etesevimab: bamlanivimab 700 mg + etesevimab 1400 mg, IV or SC once

Intravenous Infusion (See tables 1&2):

- Bamlanivimab and etesevimab are both available as solutions in separate vials and must be diluted and combined prior to administration.
- To prepare the dose you will need 1 vial of bamlanivimab and 2 vials of etesevimab.
- Administer bamlanivimab and etesevimab together as a single IV infusion via pump or gravity
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

Storage: Refrigerate unopened vials at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze, shake, or expose to direct light. The diluted infusion solution should be administered immediately. If immediate administration is not possible, the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C) and up to 7 hours at room temperature (20°C to 25°C) including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.

Warnings/ Adverse Events

Serious and unexpected adverse events may occur with use of bamlanivimab and etesevimab including:

- Hypersensitivity including Anaphylaxis and Infusion-Related reactions may occur
  Examples: fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (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, vasovagal reactions (e.g., pre-syncope, syncope), dizziness and diaphoresis.
- In some cases, clinical worsening may occur after Bamlanivimab and Etesevimab administration

Distribution and Monitoring Usage of Bamlanivimab and Etesevimab in Nepal

- The MoHP will coordinate with the Department of Health Services Management Division for distribution and delivery of the drug based on the current and projected patient loads.
- The NHRC and DDA will monitor and collect data on side effects and outcome through electronic methods.

Table 1: 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.

Table 2: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion 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 60 mL to an 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).

References:

1. Fact sheet for health care providers emergency use authorization (EUA) of bamlanivimab and etesevimab, September 16, 2021
2. NIH: COVID-19 Treatment Guidelines. Updated: September 15, 2021.
3. IDSA Guidelines on the Treatment and Management of Patients with COVID-19. Last updated, 9/14/2021.
4. Planas, D., Veyer, D., Baidaliuk, A. et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature 596, 276–280 (2021).
5. CDC: SARS-CoV-2 Variant Classifications and Definitions. Updated Sept. 17, 2021.
6. The COVID-19 Treatment Guidelines Panel's Statement on Bamlanivimab Plus Etesevimab for the Treatment of Mild to Moderate COVID-19 in Nonhospitalized Patients. Last Updated: September 15, 2021
7. Dougan M, Nirula A, Azizad M, eat al; BLAZE-1 Investigators. Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19. N Engl J Med. 2021 Jul 14:NEJMoa2102685.

Government of Nepal
Ministry of Health
Department of Drug Administration

Adverse Drug Reactions Reporting Form

Hospital record No. or chart No. or patient ID No. _____

Patient's Name: _____ **Sex: F/ M** **Age** _____

Description of the adverse reaction/s: **Onset date of reaction:** _____

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Information on Suspected Medicine				
Medicines (Brand & Generic Name, Manufacturer, Batch No., Dosage Form)	**Daily dosage**	**Date started**	**Date stopped**	**Reason for use**

Additional relevant information (eg. medical history, test result, known allergies, drug interactions)

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Reported by: Name:_____ Hospital / Department:_____

Date: _____ Signature: _____

Please submit this form to your local Drug Information Unit or Hospital Pharmacy. Thank you for taking the time to fill in this report!