Treatment Plan for COVID-19 in Adults at CMH Using Baricitinib (Olumiant)

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of baricitinib for treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Baricitinib is FDA-approved for treatment of rheumatoid arthritis, however, it is not approved for the treatment of COVID-19.

As a healthcare provider, you must comply with the mandatory requirements of the EUA

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that baricitinib may be effective for treatment of COVID-19 in certain patients as specified in this Fact Sheet. You may be contacted and asked to provide information to help with the assessment of the use of the product during this emergency

Baricitinib is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of baricitinib under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner

For the most up to date Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) for Baricitinib, and Fact Sheet for Patients, Parents and Caregivers: Emergency Use Authorization (EUA) of Baricitinib for Coronavirus Disease 2019 (COVID-19) please visit https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization

Purpose:
Define the criteria and provide guidance to providers for the use of Baricitinib at CMH for the treatment of COVID-19 in hospitalized Adult patients. Please note this treatment plan is only intended for treatment of adult, please see the FDA Fact sheet for Healthcare providers for more information on use in pediatric patients.

Mechanism of Action:
Baricitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Immunosuppression induced by this class of drugs could potentially reduce the inflammation and associated immunopathologies observed in patients with COVID-19. Additionally, JAK inhibitors, particularly baricitinib, have theoretical direct antiviral activity through interference with viral endocytosis, potentially preventing entry into and infection of susceptible cells.

Approved Available Alternatives:
For the most up to date information on adequate, approved and available alternatives to baricitinib information on treatments can be found at:

- https://www.cdc.gov/coronavirus/2019-ncov/index.html
- https://www.covid19treatmentguidelines.nih.gov/
- 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:

Inclusion criteria:

- Confirmed COVID-19 (per EUA)
- Hospitalized Adult or pediatric patient (2 years of age and older) (Per EUA)
- Require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO (Per EUA)
- Requires Infectious disease approval for use
- Patients must have an eGFR, aminotransferases, and CBC with differential determined prior to first administration of baricitinib. (Per EUA)
    - Use not recommended with eGFR < 15 mL/min/1.73 m2 or dialysis,
    - There is limited information regarding use in patients with COVID-19 and any of the following: ALC <200 cells/uL, ANC < 1000 cells/uL, and Hemoglobin <8 g/dL
- Not recommended for patients with known active tuberculosis (per EUA)

Exclusion criteria:

- See Warnings and Precautions

Use in Specific Populations

- Pregnancy: Baricitinib should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. Consistent with the mechanism of action, embryo-fetal toxicities including skeletal anomalies and reduced fertility have been observed in animals dosed in excess of the maximum human exposure. The limited human data on use of baricitinib in pregnant women are not sufficient to inform a drug-associated risk for major birth defects or miscarriage
- Pediatric use: Limited data informing baricitinib dosing in pediatric patients comes from ongoing clinical trials for other uses. Please note this treatment plan is only intended for treatment of adult, please see the FDA Fact sheet for Healthcare providers for more information on use in pediatric patients.
    - It is recommended that there be a discussion with a Pediatric ID specialist before using. The outpatient on-call provider at Maine Medical Partners Pediatric Specialty Care can be reached at 207-662-5522
- Renal Impairment: There are limited data for baricitinib in patients with severe renal impairment.
    - Use not recommended for patients who are on dialysis, have end-stage renal disease (ESRD, EGFR <15 mL/min/1.73 m2), or have acute kidney injury

  - Baricitinib should only be used in adults with eGFR 15 to <30 mL/min/1.73 m2 if the potential benefit outweighs the potential risk.
  - See Table 1 for treatment modifications
- Hepatic Impairment: Baricitinib has not been studied in patients with severe hepatic impairment. Baricitinib should only be used in patients with severe hepatic impairment if the potential benefit outweighs the potential risk. It is not known if dosage adjustment is needed in patients with severe hepatic impairment. See Table 1.

Warnings and Precautions

- Serious Infections:
  - There is limited information regarding use of baricitinib in patients with COVID-19 and concomitant active serious infections.
  - Serious infections have occurred in patients receiving baricitinib:
    - Avoid the use of baricitinib with known active tuberculosis.
    - Consider if the potential benefits outweigh the potential risks of baricitinib treatment in patients with active serious infections other than COVID-19 or chronic / recurrent infections.
- Thrombosis
  - Serious venous thrombosis, including pulmonary embolism, and serious infections have been observed in COVID-19 patients treated with baricitinib and are known adverse drug reactions of baricitinib.
  - In hospitalized patients with COVID-19, prophylaxis for VTE is recommended unless contraindicated. If clinical features of deep vein thrombosis/pulmonary embolism occur, patients should be evaluated promptly and treated appropriately
- Abnormal laboratory values
  - There is limited information regarding use of baricitinib in patients with COVID-19 and any of the following clinical findings:
    - ANC <1000 cells/mm3
    - ALC <200 cells/mm3
    - Hemoglobin <8 g/dL
  - Evaluate at baseline and thereafter according to local patient management practice. Monitor closely when treating patients with abnormal baseline and post-baseline laboratory values
- Vaccines
  - Avoid use of live vaccines with baricitinib
- Hypersensitivity:
  - If a serious hypersensitivity occurs, discontinue baricitinib while evaluating the potential causes of the reaction

- Malignancies
    - Lymphoma and other malignancies have been observed in patients treated with baricitinib for treatment of Rheumatoid arthritis. Risk when used for treatment of COVID-19 unknown
- Gastrointestinal Perforations
    - Events of gastrointestinal perforation have been reported in clinical studies with baricitinib for treatment of rheumatoid arthritis , although the role of JAK inhibition in these events is not known. used with caution in patients who may be at increased risk for gastrointestinal perforation. Risk when used for treatment of COVID-19 unknown
- Immunosuppression:
    - Consider avoiding use in patients who are significantly immunosuppressed, particularly in those with recent use of other biologic immunomodulating drugs

Dosing:

- The recommended dosage in adults with eGFR ≥60 mL/min/1.73 m2 is 4 mg once daily for 14 days of total treatment or until hospital discharge, whichever is first. See Table 1 for dosage adjustments for patients with laboratory abnormalities, including renal impairment.
- Dosage adjustments in patients with renal or hepatic impairment are recommended (see Renal Impairment, Hepatic Impairment and Table 1)
- Dosage adjustments due to drug interactions are recommended (see Drug Interactions).

Drug Interactions:

- Strong OAT3 Inhibitors:
    - Baricitinib exposure is increased when baricitinib is co-administered with strong OAT3 inhibitors (such as probenecid). In patients taking strong OAT3 inhibitors, such as probenecid, reduce the recommended dose as follows:
        - If the recommended dose is 4 mg once daily, reduce dose to 2 mg once daily.
        - If the recommended dose is 2 mg once daily, reduce dose to 1 mg once daily.
        - If the recommended dose is 1 mg once daily, consider discontinuing probenecid
- Other JAK Inhibitors or biologic disease modifying anti-rheumatic drugs (DMARDs)
    - Baricitinib has not been studied in combination with other JAK inhibitors or with biologic DMARDs (biologic treatments targeting cytokines, B-cells, or T-cells) and is not recommended.

Monitoring Parameters:

- Laboratory Monitoring: Patients must have an eGFR, aminotransferases, and CBC with differential determined prior to first administration of baricitinib.
    - Evaluate at baseline and periodically thereafter. Lymphocyte, neutrophil, platelet count, hemoglobin and LFTs.
    - See Table 1 for dosage adjustments for patients with laboratory abnormalities.
- Signs and symptoms of infection (prior to, during, and after therapy)
- Monitor for clinical features of deep vein thrombosis/pulmonary embolism

- New onset abdominal symptoms
- Monitor for hypersensitivity reactions, including anaphylaxis

Additional Physician Requirements:

- Healthcare provider MUST:
  - Receive approval for use from Infectious Disease
  - Obtain written consent using the CMH drug specific consent form
    - Copy to be faxed to pharmacy
  - Complete patient Inclusion/Exclusion Checklist
    - Copy to be faxed to pharmacy
- Patient Counseling Information:
  - As the healthcare provider, you must communicate to your 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 baricitinib, including:
    - FDA has authorized the emergency use of baricitinib to treat COVID-19 in hospitalized adults and pediatric patients 2 years or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). This is not an FDA-approved use of baricitinib.
    - The patient or parent/caregiver has the option to accept or refuse baricitinib.
    - The significant known and potential risks and benefits of baricitinib, 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.
  - If providing this information will delay the administration of baricitinib to a degree that would endanger the lives of patients, the information must be provided to the patients as soon as practicable after baricitinib is administered
- Must document in the patient's medical record that the patient/caregiver has been:
  - Given the "Fact Sheet for Patients, Parents and Caregivers",
  - Informed of alternatives to receiving authorized baricitinib, and
  - Informed that baricitinib is an approved drug that is authorized for the unapproved use under this Emergency Use Authorization
- Patients must have an eGFR, aminotransferases, and CBC with differential determined prior to first administration of baricitinib
- Monitor closely patients with abnormal baseline and post-baseline laboratory values. See Table 1 for dosage adjustments for patients with laboratory abnormalities.
- The prescribing healthcare provider and/or the provider's designee are/is responsible for mandatory reporting of all medication errors and all serious adverse events* potentially related to baricitinib treatment within 7 calendar days from the onset of the event. The reports should

include unique identifiers and the words "Baricitinib treatment under Emergency Use Authorization (EUA)" in the description section of the report.

- Report of all serious adverse events and medication errors potentially related to baricitinib within 7 calendar days from the onset of the event
    - See Reporting Section for additional information on how to report
    - Provide mandatory responses to requests from FDA for information about adverse events and medication errors associated with baricitinib

Reporting of Medication Errors and Serious Adverse Events:

- The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events and medication errors potentially related to baricitinib within 7 calendar days from the onset of the event
- The prescribing health care provider and/or the provider's designee is/are to provide mandatory responses to requests from FDA for information about adverse events and medication errors associated with baricitinib

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 baricitinib 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 baricitinib	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
   - Jennifer Chase chaseje@cmhc.org

(2) Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:
   - Complete and submit the report online: www.fda.gov/medwatch/report.htm
   - Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
   - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
   - Fax to 1-800-FDA-0178, or
   - Call 1-800-FDA-1088 to request a reporting form

(3) In addition, provide 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

Table 1: Dosage Adjustments for Patients with Abnormal Laboratory Values[a, b]

Laboratory Analyte	Laboratory Analyte Value	Recommendation
eGFR	≥60 mL/min/1.73 m^2	• Adults and pediatric patients 9 years of age and older: 4 mg once daily • Pediatric patients 2 years to less than 9 years of age: 2 mg once daily
	30 to <60 mL/min/1.73 m^2	• Adults and pediatric patients 9 years of age and older: 2 mg once daily • Pediatric patients 2 years to less than 9 years of age: 1 mg once daily
	15 to <30 mL/min/1.73 m^2	• Adults and pediatric patients 9 years of age and older: 1 mg once daily • Pediatric patients 2 years to less than 9 years of age: Not recommended
	<15 mL/min/1.73 m^2	Not recommended
Absolute Lymphocyte Count (ALC)	≥200 cells/μL	Maintain dose
	<200 cells/μL	Consider interruption until ALC is ≥200 cells/μL
Absolute Neutrophil Count (ANC)	≥500 cells/μL	Maintain dose
	<500 cells/μL	Consider interruption until ANC is ≥500 cells/μL
Aminotransferases	If increases in ALT or AST are observed and drug-induced liver injury (DILI) is suspected	Interrupt baricitinib until the diagnosis of DILI is excluded

[a] Abbreviations: ALC = absolute lymphocyte count, ALT = alanine transaminase, ANC = absolute neutrophil count, AST = aspartate transaminase, DILI = drug induced liver injury, eGFR = estimated glomerular filtration rate.

[b] If a laboratory abnormality is likely due to the underlying disease state, consider the risks and benefits of continuing baricitinib at the same or a reduced dose.

References:

- US Food and Drug Administration (FDA). Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) of Baricitinib. FACT SHEET FOR HEALTHCARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF BARICITINIB (fda.gov) Published July 28, 2021. Accessed September 23, 2021
- National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated September 15, 2021. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed September 23, 2021.
- Olumiant (baricitinib) [prescribing information]. Indianapolis, IN: Lilly USA LLC; July 2020