Indian Health Service
National Pharmacy and Therapeutics Committee
COVID-19 Emerging Treatments Update

November 25, 2020

Baricitinib (Olumiant®) in combination with Remdesivir

- EMERGENCY USE AUTHORIZATION -

Mechanism of action[1,2]:
Baricitinib is a Janus kinase inhibitor, currently FDA-approved for the treatment of adult patients with moderate-to-severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor antagonist therapies. Baricitinib appears to have anti-viral effects through its affinity for certain AP2-associated proteins, thereby reducing SARS-CoV-2 endocytosis.

Current Status[1,3]:
Baricitinib has not been approved by the FDA for the treatment of COVID-19. The FDA has issued an Emergency Use Authorization (EUA) to permit the prescribing of baricitinib, in combination with remdesivir, for treatment of suspected or laboratory-confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). **Note that remdesivir is currently FDA-approved for adults and pediatric patients 12 years of age and older and weighing at least 40 kg (Remdesivir FDA Approval). Also note that safety and effectiveness of baricitinib in pediatric patients has not been established for its FDA-approved indication.**

Availability:
Baricitinib is commercially available through McKesson. Please contact McKesson and inform them of your anticipated monthly utilization to ensure that your local distribution center has adequate stock of the product. If you use a different Pharmaceutical Prime Vendor other than McKesson, please contact your account manager for information on how to proceed accordingly.

Efficacy[4,5]: Results from NIH/NIAID-sponsored Adaptive COVID-19 Treatment Trial (ACTT-2); *NCT04401579*	
****ACTT-2 Study in Hospitalized Adults Diagnosed with COVID-19 Infection**** (Currently unpublished)	
Design:	Double-blinded RCT of hospitalized adults with SARS-CoV-2 infection comparing treatment with baricitinib (BARI) plus remdesivir (N=515) with placebo plus remdesivir (N=518).
Patients:	Mean age: 55 years, 55% required supplemental 0_2; 21% on high-flow 0_2; 11% ECMO or mech. vent
1º outcome:	Median Time to recovery: **7 days** (BARI) vs **8 days** (placebo); HR: 1.15, 95% CI:1.00-1.31; *p*=0.047
2º outcome:	Improved clinical status at Day 15: **Results favored BARI**; OR: 1.26, 95% CI: 1.01-1.57; *p*=0.044
2º outcome:	Death or ↓ clinical status at Day 29: **23%** (BARI) vs **28%** (PCB); OR 0.74, 95% CI: 0.56-0.99; *p*=0.039

Adverse Drug Events / BOXED WARNINGS[4,6]:
Adverse Events rates and Risk Differences reported from the ACTT-2 Study, including (1) Serious Adverse Events, (2) Grade 3-4 Adverse Events and (3) Adverse Events leading to discontinuation of the study drug, were all similar or lower in the BARI group, with exception of venous thromboembolism and pulmonary embolism.

Thrombosis, including deep venous thrombosis and pulmonary embolism, has been observed at an increased incidence in patients treated with baricitinib compared to placebo. In addition, there were cases of arterial thrombosis. Many of these adverse events were serious and some resulted in death.

Patients treated with baricitinib are at risk for developing serious infections (e.g., active tuberculosis, invasive fungal infections) that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Lymphoma and other malignancies have been observed in patients treated with baricitinib.

Avoid use of live vaccines with baricitinib. Update immunizations in agreement with current immunization guidelines prior to initiating baricitinib therapy.

Dosing & Patient Selection[4]:

Baricitinib is administered orally. The recommended dosage of baricitinib under the EUA is:

- Adults and pediatric patients 9 years of age and older: 4 mg once daily (total of 14 days or until discharge)
- Pediatric patients 2 years to less than 9 years of age: 2 mg once daily (total of 14 days or until discharge)

Dosage adjustments are recommended for laboratory abnormalities, including renal & hepatic impairment. *In adults hospitalized patients with COVID-19, prophylaxis for venous thromboembolism is recommended unless contraindicated*. Dosage adjustments due to drug interactions are also recommended.

During patient selection;

- Evaluate baseline eGFR, liver enzymes, and CBC to determine treatment suitability and dose.
- Monitor closely patients with abnormal baseline and post-baseline laboratory values.
- Baricitinib is NOT recommended for:
  - Patients on dialysis, with end-stage renal disease, acute kidney injury or known active tuberculosis

There is limited information on baricitinib use in combination with systemic corticosteroids for treating patients with COVID-19. However, use of baricitinib in patients receiving systemic corticosteroids is not precluded.

Mandatory Requirements under the EUA[4]:

1. Treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO.
2. As the healthcare provider, communicate to your patient or parent/caregiver information consistent with the "Fact Sheet for Patients, Parents and Caregivers" prior to the patient receiving baricitinib. Healthcare providers (to the extent practicable given the circumstances of the emergency) must document in the patient's medical record that the patient/caregiver has been:
   a. Given the "Fact Sheet for Patients, Parents and Caregivers",
   b. Informed of alternatives to receiving authorized baricitinib, and
   c. Informed that baricitinib is an approved drug that is authorized for the unapproved use under this EUA
3. Patients must have an eGFR, aminotransferases, and CBC with differential determined prior to first administration of baricitinib.
4. 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 onset of the event.
   - *Should include the words "Baricitinib treatment under EUA" in the "Describe Event" section.*
   - *Should include the words "Indian Health Service" or "IHS" on the form in the reporter section (section G).*
   - Information on the FDA MedWatch program can be found on the IHS Pharmacovigilance website.

References:

1. U.S. Food and Drug Administration. Letter of Authorization. Emergency Use Authorization (EUA) for baricitinib.
2. Richardson P, Griffin I, Tucker C. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020;395:e30–e31.
3. IHS National Pharmacy and Therapeutics Commitee. FDA Approval: Remdesivir. COVID-19 Clinical Information webpage. Accessed Nov 25th, 2020.
4. U.S. Food and Drug Administration. Fact Sheet for Healthcare Providers. Emergency Use Authorization (EUA) for baricitinib.
5. U.S. National Library of Medicine. ClinicalTrial.gov NCT04401579. Accessed Nov 24, 2020.
6. OLUMIANT (baricitinib). PRODUCT INFORMATION. Eli Lilly and Company. Marketed by Lilly, USA, LLC. Indianapolis, IN 46285. USA.
7. U.S. Food and Drug Administration. Fact Sheet for Patients, Parents and Caregivers. Emergency Use Authorization for baricitinib.