FORMULARY MONOGRAPH

Baricitinib (Olumiant®)
[Eli Lilly and Company]

REQUEST

P&T reviewed on 01/07/2021: Recommended to keep non-formulary for COVID-19 requests

THERAPEUTIC USE

- Drug Class: Antirheumatic agent, Janus kinase (JAK) inhibitor
- Population Served*: Hospitalized adult and pediatric patients (2 years of age or older)

BACKGROUND[1,2,3]

- Baricitinib is a selective JAK 1 and 2 inhibitor currently approved by the FDA for the treatment of patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies
- The US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for baricitinib in combination with remdesivir for the treatment of COVID-19 on November 19th, 2020 and this was updated on July 28th, 2021
- The EUA states that Baricitinib alone is now authorized for the treatment of COVID-19 in hospitalized adults and pediatric patients two years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).
- IDSA Guidelines (last updated June 25, 2021)
    - Baricitinib is suggested in hospitalized adults with severe* COVID-19 having elevated inflammatory markers but not on mechanical ventilation
    - Baricitinib is suggested to be used in combination with remdesivir in hospitalized patients with severe* COVID-19 who cannot receive a corticosteroid
    - *Severe illness is defined as patients with SpO2 ≤94% on room air, including patients on supplemental oxygen, oxygen through a high-flow device, or non-invasive ventilation.
- NIH Guidelines (last updated July 8, 2021)
    - Baricitinib or tocilizumab can be added to standard-of-care (SOC) in hospitalized patients within 3 days of hospital admission with rapidly increasing oxygen needs, increased markers of inflammation, and requiring high-flow oxygen or non-invasive ventilation but not on mechanical ventilation or ECMO
    - Guideline recommends against use of baricitinib in combination with tocilizumab for COVID-19, except in a clinical trial

CLINICAL PHARMACOLOGY and MECHANISM OF ACTION[4]

Baricitinib inhibits JAK enzymes, which are intracellular enzymes involved in stimulating hematopoiesis and immune cell function through a signaling pathway. In response to extracellular cytokine or growth factor signaling, JAKs activate signal transducers and activators of transcription (STATs), which regulate gene expression and intracellular activity. Inhibition of JAKs prevents the activation of STATs and reduces serum IgG, IgM, IgA, and C-reactive protein.

FDA APPROVED INDICATIONS*[4]

- Treatment of moderately to severely active rheumatoid arthritis in patients who have had an inadequate response to one or more TNF antagonist therapies (2018)

POTENTIAL UNLABELED USE / OFF LABEL USE*[1]

- Treatment of COVID-19 in hospitalized patients requiring high-flow oxygen, invasive mechanical ventilation, or ECMO in combination with remdesivir

PROCUREMENT & STORAGE[4]

Formulation	Storage
Tablet, oral: 1 mg and 2 mg	Store at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted to 15ºC to 30ºC (59ºF to 86ºF)

HAZARDOUS CLASSIFICATION[4,5]

- Non-hazardous

DOSAGE & ADMINISTRATION (Table below is for Epic Willow build)

Order Build Elements:	IT Build Notes (use N/A where necessary):
Name and strength of all units needing to be built for dispensation	Baricitinib (Olumiant®) 1 mg, 2 mg
Default Dose	4 mg
Dose Buttons	1 mg, 2 mg, 4 mg
How should doses be rounded? (1, 0.1, 0.01 to the nearest mcg, mg, etc.)	N/A
Should the oral dosage form in Epic be built with the ability to order half doses ie: are half tablet doses clinically relevant?	No
Available Routes (this allows IT to exclude routes in look up not appropriate for use)	Oral, feeding tube, Specified Tube (See order Question)
Default Route	Oral
Route Buttons (Radial Buttons to add)	Oral
Default Frequency	Once daily
Frequency Buttons	N/A
PRN Reasons	N/A
Default Duration	14 days
Duration Buttons	N/A

Comments- Pharmacy notes	N/A
MAR Administration Instructions	May be administered with or without food. If patient unable to swallow tablets whole, the tablet may be chewed. Tablet may be placed in a container containing 5 to10 mL of room temperature water and gently dispersed by swirling. The entire mixture must be consumed immediately. The container should be rinsed with an additional 10 mL and contents swallowed. **Gastrostomy feeding tube**: Same as above except container should contain approximately 15 mL of water. Withdraw entire contents from container with an appropriate syringe and immediately administer through gastric feeding tube. Rinse container with 15 mL of water, withdraw contents into the syringe and administer through the tube. **Nasogastric feeding tube:** Same as above, except tablet should be dispersed in 30 mL of water and rinsed with at least 15 mL of water.
Order Instructions	None
Label Comments	N/A
Proportion of Days Covered (PDC) Class	N/A

DOSING & DOSE ADJUSTMENTS

- The recommended dosage in adults with eGFR ≥ 60 mL/min/1.73 m^2 is 4 mg once daily for 14 days of total treatment or until hospital discharge, whichever is first. See table below for dosage adjustments for patients with laboratory abnormalities.
- The recommended dosage for patients 9 years of age and older is 4 mg once daily for 14 days of total treatment or until hospital discharge, whichever is first.
- The recommended dosage for patient ages 2 through less than 9 years of age is 2 mg once daily for 14 days of total treatment or until hospital discharge, whichever is first.
- Baricitinib is not authorized for patients younger than 2 years or age.

Laboratory Analyte	Laboratory Analyte Value	Recommendation
eGFR	≥ 60 mL/min/1.73 m^2	• Adults and pediatric patients ≥ 9 years of age: 4 mg once daily • Pediatric patients 2 years to < 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: 2 mg once daily • Pediatric patients 2 years to < 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: 1 mg once daily • Pediatric patients 2 years to < 9 years of age: Not recommended
	<15 mL/min/1.73 m^2 and End stage renal disease (ESRD) on HD	• 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

PHARMACOKINETICS [4,6]

Metabolism	Hepatic metabolism, primarily CYP3A4
Bioavailability	~80%
Elimination	Urine: ~75% (69% unchanged drug); feces ~20% (15% unchanged drug)
Half-life ($t_{1/2}$)	~12 hours

PHARMACOKINETICS IN SPECIAL POPULATIONS[4,6]

Special Population	Systemic Availability
Gender (females)	• No dose adjustments recommended
Elderly - **age** > **65 years**	• No dose adjustments recommended. Monitor renal function.
Pediatric - age <18 years	• See table above for dose adjustments
Renal Impairment	• AUC increased by 1.41-, 2.22-, 4.05-, and 2.41-fold for mild, moderate, severe renal impairment, and ESRD with hemodialysis, respectively • See table above for dose adjustments
Hepatic Impairment (Moderate Impairment)	• AUC and C_{max} increased by 1.19- and 1.08-fold, respectively • No dosage adjustment necessary for mild to moderate impairment at initiation • Not studied in severe hepatic impairment. Use is not recommended

PREGNANCY SUMMARY & USE IN BREAST FEEDING[4,6]

- Pregnancy: There is limited data on the use of baricitinib in pregnant women. In animal embryo-fetal development studies, oral baricitinib was administered to pregnant rats and rabbits at exposures equal to and greater than approximately 20 and 84 times the maximum recommended human dose (MRHD), respectively, resulted in reduced fetal body weights, increased embryo lethality (rabbits only), and dose-related increases in skeletal malformations. No developmental toxicity was observed in pregnant rats and rabbits treated with oral baricitinib during organogenesis at approximately 5 and 13 times the exposure at the MRHD, respectively. In a pre- and post-natal development study in pregnant female rats, oral baricitinib administration at exposures approximately 43 times the MRHD resulted in reduction in pup viability (increased incidence of stillborn pups and early neonatal deaths), decreased fetal birth weight, reduced fetal body weight gain, decreased cytotoxic T cells on post-natal day (PND) 35 with evidence of recovery by PND 65, and developmental delays that might be attributable to decreased body weight gain. No developmental toxicity was observed at an exposure approximately 9 times the exposure at the MRHD. Baricitinib should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and fetus**.**
- Lactation: There is no available data on the presence of baricitinib in human milk, the effects of the drug on a breastfed infant, or the effects of drug on milk production. Baricitinib is present in the milk of lactating rats, for which the clinical relevance of this data is not clear. Due to the potential for serious adverse reactions in nursing infants, breastfeeding is not recommended by the manufacturer.

ADVERSE DRUG EVENTS / EFFECTS*[4]

- Most common adverse reactions (>10%) include infection (29%; serious infection: 1%) and upper respiratory tract infection (16%). Other side effects include nausea (3%), increases in AST/ALT (1-2%), and herpes zoster infection (1%).

CONTRAINDICATIONS[4,6]

- None

MEDICATION SAFETY ASSESSMENT & RECOMMENDATIONS[4,6]

- **Black Box Warnings:**
  - **Serious Infections:** Patients receiving baricitinib are at an increased risk for serious infections, which may result in hospitalization and/or fatality. Serious infections reported include active tuberculosis, invasive fungal and pneumocystosis, and bacterial, viral, or other opportunistic infections. Most patients who developed these infections were taking concomitant immunosuppressive agents. If a serious infection develops, interrupt baricitinib until infection is controlled. Do not initiate baricitinib in patients with active, serious infections, including localized infections.
  - **Malignancies:** Lymphoma and other malignancies have been observed in patients receiving baricitinib. Consider risk versus benefits prior to using in patients with known malignancy.
  - **Thrombosis:** Thrombosis, including deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis have been observed and may be serious and life-threatening. Promptly evaluate new onset-symptoms of DVT, PE, or arterial thrombosis and treat appropriately. Use with caution in patients with an increased risk of thrombosis. Prophylaxis for VTE is recommended in patients hospitalized with COVID-19 unless contraindicated.
  - **Tuberculosis (TB):** TB has been reported in patients receiving baricitinib. Patients should be evaluated for latent TB infection prior to and during therapy. If positive, start treatment for latent TB prior to use. Avoid use in patients with known active TB.
- **Sentinel Events Advisories posted*:** None found
- **High Alert/SALAD:** No sound alike or look alike drugs identified and not needed to be added to the high alert list
- **Dual Sign/Witness:** Not needed
- **Monitoring:**
  - Monitor at baseline eGFR, liver enzymes, and complete blood count and adjust dosing as needed. (see **DOSAGE AND DOSE ADJUSTMENTS** section)
- **Significant 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 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 DMARDS: Baricitinib has not been studied in combination with other JAK inhibitors or with biologic DMARDs.
- **REMS requirements:** None

- **Warnings and Precautions:** In addition to the Black Box Warnings above,
    - If a serious hypersensitivity occurs, discontinue baricitinib while evaluating potential causes of reaction.
    - Avoid use of live vaccines with baricitinib.
    - Gastrointestinal (GI) perforations: Use with caution in patients at an increased risk for GI perforation (ex: history of diverticulitis). Promptly evaluate new-onset abdominal symptoms in patients taking baricitinib.
    - Hematologic toxicity: Lymphopenia, anemia, and neutropenia may occur and is generally reversible and managed by treatment interruption. Do not initiate therapy in patients with an ALC <500 cells/mm^3, ANC <1,000 cells/mm^3, or hemoglobin <8 g/dL. Monitor at baseline and periodically thereafter.
    - Hepatic effects: Increased incidence of liver enzyme elevations (≥5 ULN for ALT and ≥10 ULN for AST) was observed in patients taking baricitinib. Monitor LFTs as clinically indicated and interrupt therapy if LFTs are increased and DILI is suspected.
    - Lipid abnormalities: Dose dependent increases in lipid parameters were observed in patients receiving baricitinib. Usually seen within 12 weeks of initiation.
- **Potential for Errors and Abuse*:** None identified
- **Other Risks*:** None identified

SIMILAR PRODUCTS BY CLASS or TREATMENT INDICATION

Available Products	Indications
N/A	**N/A**

THERAPEUTIC EFFECTIVENESS*[7,8]

Citation	Design*	Study Population	Outcomes	Critique & Interpretation
ACTT-2 Trial	Randomized, double-blind, placebo-controlled trial (n=1033) Barcitinib 4 mg once daily up to 14 days + remdesivir x 10 days vs. Placebo x 14 days + remdesivir x 10 days	• Adult patients hospitalized with COVID-19 • Patients excluded if anticipated discharge within 72 hours, received steroids (unless for ARDS, septic shock, etc.), immunocompromised	Decreased time to recovery by 1 day (7 versus 8 days, RRR 1.16; 95% CI, 1.01-1.32) Decreased time to recovery by 8 days in receiving high-flow oxygen (HFO) or noninvasive ventilation (NIV) (10 days vs 18 days, rate ratio 1.51; 95% CI 1.10 to 2.08) 28-day mortality (5.1% vs 7.8%, HR 0.65;95% CI, 0.39-1.09)	• Baricitinib decreases time to recovery in COVID-19, benefit was most apparent in patients on HFO/NIV • Excluded patients receiving steroids • No mortality benefit noted

COV-BARRIER (medRxiv preprint)	Multinational, randomized, placebo-controlled trial (n=1,525) Baricitinib 4mg once daily up to 14 days + SOC vs. SOC	• Hospitalized patients >18 years old with symptomatic COVID-19 • Patients excluded if requiring IMV, immunosuppressed, or received convalescent plasma or IVIG • Corticosteroids in 79%, remdesivir in 18.9%	Disease progression at 28 days: 27.7% vs 30.5% (OR 0.85; 0.67 to 1.08) 28-day mortality: 8.1% vs 13.1% (HR 0.57; 95% CI 0.41 to 0.78) SAEs: 14.7% vs 18.0% (RR 0.82; 95% CI 0.65 to 1.03)	• Number needed to treat (NNT) with baricitinib to prevent 1 additional death was 20 • NNT = 9 for HFO/NIV subgroup • Mortality reduction also seen across baseline corticosteroid use and NIH ordinal scale subgroups

VALUE ANALYSIS/ FINANCIAL ANALYSIS OF COST OF THERAPY

Treatment Regimen	Cost*	Cost per course
Baricitinib 4mg for up to 14 days	$2,265 per #30 of 2 mg baricitinib	$2,114
Tocilizumab 8mg/kg x1	$1,152 per 200 mg vial $2,767 per 400 mg vial	$2,767 per 400 mg dose $3,457 per 600 mg dose $5,534 per 800 mg dose
Remdesivir 200 mg on day 1, then 100 mg for total 5 days	$520.00 per vial	$3,120

* wholesale acquisition cost (WAC)

Anticipated number of patients/month	Anticipated future 6-month cost
2-10	$25,728 - $128,640

OVERALL SUMMARY AND RECOMMENDATION

Baricitinb is a JAK 1 and 2 inhibitor hypothesized to have both anti-inflammatory as well as potential anti-viral properties in the treatment of COVID-19. Publication of the first randomized controlled trial (RCT), ACTT-2, led to the initial EUA issuance in November 2020.

ACTT-2 compared baricitinib combined with remdesivir against remdesivir monotherapy in hospitalized patients with COVID-19 and found that combination therapy decreased time to recovery by one day. Improvement in time to recovery was most apparent in patients receiving high-flow oxygen (HFO) or noninvasive ventilation (NIV), where recovery time was shortened by 8 days (10 days vs 18 days, rate ratio 1.51; 95% CI 1.10 to 2.08). No statistically significant difference was found in mortality between groups. Patients who were concurrently on steroids were excluded from the study.

COV-BARRIER, available only as a non-peer reviewed preprint, included patients with COVID-19 who required supplemental oxygen at enrollment but not invasive mechanical ventilation (IMV). This trial compared baricitinib versus standard of care and found no difference for the primary outcome of disease progression at 28 days. However, 28-day mortality was reduced by 38.2% in the baricitinib arm (8.1% vs 13.1%; hazard ratio [HR] 0.57; 95% CI 0.41-0.78; p = 0.002). In subgroup analysis, patients on HFO or NIV at baseline demonstrated a statistically significant mortality benefit (17.5% vs 29.4%; HR 0.52, 95% CI 0.33-0.80; nominal p=0.007). Importantly, 79% of patients received steroids while only 18.9% received remdesivir in this study.

Based on the results in both trials, baricitinib has demonstrated the most apparent benefit in patients on HFO or NIV. The EUA was updated on July 28th to reflect the findings from the studies, allowing baricitinib to be used alone for COVID-19. Tocilizumab, an IL-6 inhibitor, has also demonstrated mortality benefit in two RCTs (REMAP-CAP and RECOVERY) which included patients with elevated markers of systemic inflammation, concurrent steroid use, and recent initiation of HFO, NIV, or MV. Studies directly comparing baricitinib and tocilizumab are not available, thus there is insufficient evidence to recommend one over the other.

Most of the data regarding adverse effects of JAK inhibitors has been documented in patients on this medication chronically. These side effects include infections, myelosuppression, hepatic toxicities, as well as a slightly higher risk of thrombotic events. However, short-term baricitinib did not show higher rates of adverse events than the comparator groups in either RCT.

Because of the paucity of consistent data, the rate at which new data is being released, as well as on-going research, we do not feel it is a reasonable expectation for staff pharmacists to be able to speak at an expert level on the use of baricitinib. This type of discussion is often required when orders do not meet restriction criteria. As such, we recommend keeping baricitinib as a non-formulary medication for the time being with all requests continuing to be reviewed by the Antimicrobial Stewardship pharmacist or physician chair prior to approval.

Recommendations for baricitinib:

Approve if:

- Confirmed COVID-19
- Patients requiring high-flow supplemental oxygen or noninvasive mechanical ventilation

Deny if:

- Patient doesn't meet clinical criteria
    - Patient is on room air
    - Patient previously/concurrently receiving tocilizumab
    - Patients on supplemental low-flow oxygen or invasive ventilation/ECMO unless contraindicated for steroids
- Significant immunosuppression, particularly in those with a history of recent use of other biologic immunomodulating drugs
- An uncontrolled, serious bacterial, fungal, or non-SARS-CoV-2 viral infection
- ALT or AST > 10 x ULN
- Neutropenia (ANC < 500 cells/microL) or lymphopenia (ALC < 200 cells/microL)
- Patients who have ESRD (eGFR < 15ml/min), or acute kidney injury, or are on dialysis

Recommended Monitoring:

- Baseline and daily monitoring of CBC, LFTs, renal function

MONOGRAPH PREPARED BY AND DATE

Wenjing Wei, Updated July 16, 2021, July 29th, 2021

Melissa Weller, December 14, 2020

*The Joint Commission Requirements MM.02.01.01 & CMS §482.25(b)(9)
(must be completed for each new drug addiction)
MM.02.01.01

EP2. The hospital develops and approves criteria for selecting medications, which, at a minimum, include the following: - Indications for use - Effectiveness - Drug interactions - Potential for errors and abuse - Adverse drug events - Sentinel event advisories - Population(s) served (for example, pediatrics, geriatrics) - Other risks – Costs. The hospital determines a method to monitor the response of the patient.

Interpretive Guidelines §482.25(b)(9)

The medical staff must establish a formulary system. The formulary lists medications for dispensing or administration that the hospital maintains or that are readily available. In accordance with accepted standards of practice, the medical staff, in consultation with the pharmacy service, should develop written criteria for determining what medications are available for dispensing or administration. At a minimum, the criteria include the indication for use, effectiveness, risks (including propensity for medication errors, abuse potential, and sentinel events), and costs.

Processes and mechanisms should be established to monitor patient responses to a newly added medication before the medication is made available for dispensing or administration within the hospital.

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