**Brand Name: Olumiant**

**Generic Name:** baricitinib

**Manufacturer:** Eli Lilly and Company

**Drug Class[1-3]:** Janus kinase 1 and 2 (JAK 1 and JAK 2) inhibitor

**Uses:**

**Labeled[1-3]:** treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.
**Unlabeled[1-3]:** none

**Mechanism of Action[1,2]:** Janus kinase (JAK) inhibitors reduce the phosphorylation and activation of signal transducers and activator of transcription responsible for cytokines and growth factors involved in hematopoiesis, inflammation, and immune function.

**Pharmacokinetics[1-3]:**

**Absorption:**

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|---|---|
| **$T_{max}$** | 1 hour |
| **$V_d$** | 76 L |
| **$T_{1/2}$** | 12 hours |
| **Clearance** | 8.9 L.hr |
| **Protein Binding** | 50% bound to plasma proteins and 45% bound to serum proteins |
| **Bioavailability** | 80% |

**Metabolism:** Around 6% of orally administered baricitinib is identified as metabolites, primarily through CYP3A4 enzyme pathways.

**Excretion:** Baricitinib is primarily excreted renally through filtration and is identified as a substrate of OAT3, Pgp, BCRP and MATE2-K from in vitro studies. Approximately 75% of the administered dose is eliminated in the urine, while about 20% of the dose is eliminated in the feces. Baricitinib was excreted predominately as unchanged drug in urine (69%) and feces (15%).

**Efficacy:**

**Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. NEJM. 2016;374(13):1243-1252.**

**Study Design:** Phase III, randomized, double-blinded, placebo controlled, 24-week multicenter study

**Description of study:** *Methods***:** 527 patients with moderate to severely active rheumatoid arthritis were enrolled from 178 centers in 24 countries and were randomized in a 1:1:1 ratio to baricitinib at a dose of 2 or 4 mg daily or placebo for 24 weeks in addition to their current treatment. Patients also had inadequate response to or unacceptable side effects from past use of TNF-inhibitors, biologic DMARDs, or both. Patients were excluded if they had a recent, clinically significant infection or abnormal laboratory results. If a patient in either treatment group had a GFR between 40 and 60 mL/min/1.73m$^2$, they were given the 2 mg dose regardless of which dose they were randomized to receive. *Outcome Measures*: The primary outcome was the proportion of patients who achieved American College of Rheumatology 20% (ACR20) response at week 12. The primary comparison was between the 4 mg dose of baricitinib and placebo. Secondary efficacy measures looked at ACR50 and ACR70 as well as various disease activity and function assessment scales. Secondary safety measures assessed the severity and incidence of adverse effects, laboratory tests and vital signs at schedule visits. *Results:* At week 12, 55% of patients receiving the 4 mg dose of baricitinib achieved ACR20 compared to 27% in the placebo group ($p < 0.001$). The 4 mg treatment group also had significant improvements in two of the scales measuring disease activity, the 28-Joint Disease Activity Score using C-reactive Protein (DAS28-CRP) and the Health Assessment Questionnaire Disability Index (HAQ-DI) ($p < 0.001$). Adverse events for each group were reported as follows: 4 mg treatment group, 77%; 2 mg treatment group, 71% and placebo treatment group, 64%. Serious adverse events occurred at rates of 4%, 10% and 7% in the 2mg, 4mg and placebo groups respectively, with the most common event being serious infection.

**Limitations:** This study mainly compared the 4 mg treatment to the placebo when the actual FDA approved dosage of baricitinib is 2 mg. There was only a 24 week follow up period which was not an extensive amount of time to evaluate the long-term safety of baricitinib. Some of the patients in the 4 mg group had a GFR between 40 and 60 mL/min/m$^2$ meaning they received the 2 mg dose but were evaluated as a part of the 4 mg treatment group which could have skewed the results. Also, the assessment of structural joint damage through radiography was not done in this trial. The trial also did not directly compare the 4 mg treatment group to the 2 mg treatment group for some outcomes. This study was funded by Eli Lilly which could introduce bias into the study design and conclusions.

**Conclusion:** Baricitinib 4 mg was found to have significant benefit compared to placebo. The results show that the use of baricitinib can have significant effects in patients with refractory rheumatoid arthritis and can be used as a standard of therapy. Solely based on this study, future research is needed to determine if the 4 mg treatment has significant greater efficacy than the 2 mg treatment because a definitive conclusion cannot be drawn based on the comparison provided.

**Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. NEJM. 2017;376(7):652-662.**

**Study Design:** Phase III, 52-week, double-blind, parallel-group, placebo-and active-controlled, multicenter trial

**Description of study:** *Methods:* Over 52 weeks, 1307 patients from 281 centers in 26 countries were randomized in a 3:3:2 ratio between placebo (switched to 4 mg of baricitinib at 24 weeks), 4 mg of baricitinib orally once daily or 40 mg adalimumab subcutaneous injection every other week. All were in combination with their current therapy including methotrexate. Patients had to be 18 years or older with active rheumatoid arthritis, an inadequate response to methotrexate, 3 or more joint erosions or 1 or more joint erosions and positive seropositivity for rheumatoid factor or anti–citrullinated peptide antibodies. Patients were excluded for previous biologic DMARD therapy, laboratory abnormalities, or recent clinical infection. Patients with a GFR between 40 and 60 mL/min/1.73m$^2$ were given a 2 mg baricitinib dose. If patients did not have a 20% reduction from baseline at both 14 and 16 weeks, they received open-label rescue treatment of 4 mg baricitinib. *Outcome Measures:* The primary endpoint assessed proportion of patients given baricitinib compared to placebo who achieved American College of Rheumatology 20% (ACR20) response at week 12. Secondary endpoints included progression of joint damage at week 24, changes in physical function and disease activity, remission rates, and patient reported outcomes. Safety was assessed by laboratory tests, vital signs and adverse event reporting. *Results:* 70% of patients receiving treatment with baricitinib achieved CR by week 12 compared to 40% of patients who received placebo ($p<0.001$) and significant changes were seen in the major secondary endpoints. Both baricitinib and adalimumab had a significant reduction in joint damage at week 24. With a noninferiority margin of 12%, baricitinib was found to be non-inferior to adalimumab at week 12 for ACR20 (baricitinib 70%; adalimumab 61%; 95% CI 2-15%). According to the statistical analysis, baricitinib is significantly superior to adalimumab ($p=0.01$). Significant improvements were also seen in the efficacy measures between baricitinib and placebo at week 1 and weeks 2 through 4 when comparing it to adalimumab. Adverse events rates by week 24 were baricitinib (71%), adalimumab (68%) and placebo (60%) with serious adverse events occurring at 5%, 2% and 5% respectively. By week 52, serious adverse events occurred in 8% of baricitinib patients and 4% of adalimumab patients.

**Limitations:** The study had a ratio of 3:3:2 which meant the adalimumab group had less patients involved in the study. This may have skewed the results and claims of superiority of baricitinib. Eli Lilly also funded this study which could introduce bias. In particular, they did not highlight the comparison to adalimumab until the discussion where they determined superiority, and there appeared to be bias in the author's conclusions.

**Conclusion:** Baricitinib did show efficacy in achieving ACR20 as well as having significant improvements in the secondary measures. Baricitinib was shown to improve patient outcomes and could be beneficial in patients who are not receiving treatment benefit with current therapies.

**Keystone EC, Taylor PC, Drescher E, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. Ann Rheum Dis. 2015;74(2):333-340.**

**Study Design:** Phase IIb, double-blinded, randomized, placebo-controlled, multicenter study

**Description of study:** *Methods:* 301 patients with moderate to severe rheumatoid arthritis were enrolled from 69 centers in 9 countries to assess the use of baricitinib despite the use of methotrexate with or without the use of conventional DMARDs. Patients were between the ages of 18 and 75 with RA for at least 6 moths and less than 15 years. Patients were excluded if they had previously used biological DMARDs, recent or concurrent infection, an estimated GFR of < 50 mL/min, or history of chronic liver disease. The patients were randomized in a 2:1:1:1:1 ratio and given a once daily dose of placebo, 1, 2, 4, or 8 mg dose of baricitinib. After 12 weeks, the placebo and 1 mg patients were re-randomized to receive 2 mg twice daily or 4 mg once daily for 12 weeks. *Outcome Measures:* The primary outcome assessed the 4 mg and 8 mg treatment groups to determine the percentage achieving ACR20 by week 12 compared to placebo. Secondary outcomes looked at ACR 50 and ACR70 as well as multiple scales assessing disease activity, the patient's global assessment and joint stiffness. Another secondary measure looked at the re-randomized group of patients during weeks 12-24. Safety assessments were also completed looking at vitals, laboratory values and physical exams. *Results:* There was a significant increase in patients in the combined baricitinib 4 mg and 8 mg dose groups who achieved ACR20 at week 12 compared to placebo (76% vs 41%, $p < 0.001$). The 1 mg, 4 mg and 8 mg groups had a significant amount of patients achieve ACR20 by week 2 ($p < 0.01$). Efficacy was maintained in the primary and secondary outcomes through week 24. Safety was addressrd and by week 12, there were similar accounts of treatment emergent adverse effects between the placebo and baricitinib groups. There was a decline in mean neutrophil count in the baricitinib groups which was more common in the 8 mg group at weeks 12 and 24. At weeks 12 and 24, the 4 mg dose provided better efficacy in achieving ACR20, ACR50, ACR70, low disease activity and remission when compared to the 2 mg dose. The 4 mg and 8 mg showed similar efficacy but the 8 mg group may increase the risk of adverse events.

**Limitations:** This study was funded by Eli Lilly who manufactures this medication. This could lead to bias when assessing the efficacy and safety. The study only lasted for 24 weeks so long term efficacy was not established. The placebo group was twice the size of the other groups for the first 12 weeks so this may have skewed the results when comparing the active treatment groups to placebo in the first 12 weeks.

**Conclusion:** This study was able to show the safety and efficacy of baricitinib at multiple doses. It was concluded that the 4 mg dose is recommended and the 8 mg dose led to more adverse effects. Currently, the FDA has only approved the 2 mg dose, but by studying the various doses, this trial provides information regarding which dose may be the most efficacious with the lowest safety risk.

**Contraindications[1,2]:** None have currently been established.

**Precautions[1]:**

**Serious Infections:** Baricitinib should be avoided in patients with any active, serious infections. Serious and sometimes fatal infections have occurred in patients while taking this medication. Common serious infection include pneumonia, herpes zoster and urinary tract infections. Stop treatment with baricitinib in patients with any serious infection occurrence, including localized infections or sepsis. Tuberculosis should be tested for prior to initiating therapy with baricitinib. If a patient has latent tuberculosis, they should be treated prior to treatment with this medication. Viral reactivation, including herpes zoster, has been reported in patients as well. Patients with viral hepatitis B or C were excluded from trials so there is no data supporting the impact baricitinib may have in these patients.

**Malignancy and Lymphoproliferative Disorders:** Compare the risks and benefits of initiating or continuing treatment with baricitinib in patients with a known malignancy or a patient who develops a malignancy while taking baricitinib. Non-melanoma skin cancers have been reported in patients taking baricitinib.

**Thrombosis:** Deep vein thrombosis, pulmonary embolism, and arterial thrombosis have been observed in patients being treated with baricitinib with most being serious and some even resulting in death. Baricitinib should be used with caution in patients who have a high risk for thrombosis.

**Gastrointestinal (GI) Perforations:** The role of JAK inhibitors in GI perforation is not known but has been reported with the use of baricitinib. Patients with increased risk for GI perforation should use caution when starting or continuing this medication.

**Laboratory Abnormalities:** Baricitinib is associated with increased incidence of neutropenia, lymphopenia, anemia, elevated liver enzymes and lipid elevations. Evaluate at baseline and periodically during treatment.

**Neutropenia:** Avoid initiation or interrupt treatment if ANC is less than 1,000 cells/$mm^3$.

**Lymphopenia:** Avoid initiation or interrupt treatment if ALC is less than 500 cells/$mm^3$.

**Anemia**: Avoid initiation or interrupt treatment if hemoglobin is less than 8 g/dL.

**Liver enzyme elevation:** 5-10 times the upper limit of normal of AST and ALT have been reported.

**Lipid elevations:** Increases in total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol have been reported.

**Vaccinations:** Avoid the use of live vaccines while taking baricitinib.

**Adverse effects [1-3]:**

**Common (>10%)**

*Respiratory*

Upper respiratory infection (16.3%)

*Other*

Infectious disease (29-59.6%)

**Infrequent (1-10%)**

*Hepatic*

Elevated AST/SGPT (1.7%)

Elevated ALT/SGOT (1.3%)

*Gastrointestinal*

Nausea (2.7%)

*Hematologic*

Increaed platelet count (1.1%)

Thrombocytosis (1.1%)

*Dermatologic*

Herpes Zoster (1%)

**Rare (<1%)**

*Hematologic*

Neutropenia (0.6%)

Arterial thrombosis (0.4-0.6%)

Venous Thromboembolism (0.4%)

*Other*

Cancer, non-melanoma (0.2-0.4%)

Herpes simplex (0.8%)

Acne vulgaris (<1%)

**Unknown Incidence**

*Hematologic*

Anemia

Lymphocytopenia

*Musculoskeletal*

Increased creatinine kinase level

*Renal*

Increased serum creatinine

**Drug Interactions [1-3]:**

**Strong OAT3 Inhibitors:** exposure to baricitinib is increased when used concomitantly with strong OAT3 inhibitors (ex. Probenecid). This can result in a 2-fold increase in baricitinib AUC.

**Other JAK Inhibitors or Biologic DMARDs:** Use of baricitinib with these medications can lead to increased risk of immunosuppression and infection.

**Dosing/Administration[1]:**

**Dosing in Rheumatoid Arthritis:** 2 mg once daily as monotherapy or in combination with methotrexate or non-biologic disease-modifying antirheumatic drugs (DMARDs).

**Dosing During Serious Infections and Cytopenias**: hold treatment of baricitinib until the infection is controlled.

**Dosing in patient with Lymphopenia:** if ALC < 500, hold until ALC $\geq$ 500.
**Dosing in patient with Neutropenia:** if ANC < 1000, hold until ANC $\geq$ 100.
**Dosing in patient with Anemia:** if hemoglobin < 8, hold until hemoglobin >8.

**Dosing in Renal Impairment:** No adjustment needed if GFR is > 60 mL/min/1.73m$^2$. Baricitinib not recommended if GFR < 60 mL/min/1.73m$^2$.

**Dosing in Hepatic Impairment:** No adjustment needed if mild/moderate hepatic impairment. Baricitinib is not recommend in patients with severe hepatic impairment.

**Use in Special Circumstances[1]:**

**Pregnancy:** Baricitinib has limited human data when studied in pregnant women. When studied in animal embryo-fetal development at exposures 20-84 times the recommended human dose, reduced fetal body weight, increased embryo lethality and dose-related increases in skeletal malformations were reported. Pre- and post-natal development studies resulted in decreased survival from birth, decreased birth weight, developmental delays and increased malrotated forelimbs. No developmental toxicities were reported.

**Lactation:** There is no available information on baricitinib in human milk or the effect it has on the infant being breastfed. Studies have shown presence of the medication in the milk of rats. For safety, it is not recommended that a breastfeeding woman be treated with baricitinib.

**Geriatric population:** There has not been a significant difference in safety or efficacy seen in patients over the age of 65 when studied. Greater sensitivity in older patients cannot be ruled out. Due to baricitinib being excreted by the kidney, older adults have a higher likelihood of decreased renal function so renal function should be monitored.

**Pediatric population:** Safety and efficacy have not be established in pediatric patients.

**Overdose:** A single dose of 40 mg and multiple doses of 20 mg over 10 days have been studied without any resulting dose-limiting toxicities. More than 90% of the dose is expected to be excreted within 24 hours. If a patient does exceed the recommended dose, monitor for adverse effects and seek treatment as needed.

**Conclusion:** When used for patients who previously had not had successful treatment with other therapies, baricitinib has been shown to have efficacy in achieving ACR20. Rheumatoid arthritis is a disease that is primarily assessed through a patient's quality of life and reports of disease burden and physical inability. There was significant improvements in multiple trials supporting the use of baricitinib compared to placebo and also compared to a biologic DMARD, adalimumab. The trial results primarily concluded that the 4 mg dose is the most efficacious without a significant increase in adverse effects, but currently only the 2 mg dose has been approved so further studies are required to determine if the 4 mg should be the standard dose used in patients. This treatment option provides an oral medication that showed efficacy in patients which would be a positive in comparison to the bi-weekly injection. Further studies need to be done comparing baricitinib to other rheumatoid arthritis therapies to assess if baricitinib could be a first line treatment in moderate to severe rheumatoid arthritis.

**Recommended References:**


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2. Baricitinib. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed September 21, 2018.
3. Baricitinib. Clinical Pharmacology [Internet database]. Gold Standard, Inc., 2007. Available at: http://www.clinicalpharmacology.com. Accessed: September 21, 2018.
4. Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. The New England Journal of Medicine. 2016;374(13):1243-1252.
5. Keystone EC, Taylor PC, Drescher E, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. Annals of the rheumatic diseases. 2015;74(2):333-340.
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