PDL DRUG REVIEW

Proprietary Name: Olumiant®
Common Name: baricitinib
PDL Category: Anti-Inflammatories, Non-NSAID

Comparable Products	Preferred Drug List Status
Enbrel	Preferred with Conditions
Humira	Preferred with Conditions
Xeljanz	Non-Preferred with Conditions

Summary

Pharmacology/Usage: Baricitinib, the active ingredient of Olumiant®, is a Janus Kinase (JAK) Inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membranes to influence cellular processes of hematopoiesis and immune cell function.

Indication: For the treatment of adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies. Use in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

There is no pregnancy category for this medication; however, the risk summary indicates that the limited human data on use in pregnant women are not sufficient to inform a drug-associated risk for major birth defects or miscarriage. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Film-Coated Tablets: 2mg

Recommended Dosage: Prior to starting treatment, test for latent tuberculosis (TB). If positive, consider treating for TB prior to Olumiant® use. Take 2mg once daily with or without food as monotherapy or in combination with methotrexate or other DMARDs. Dose adjustments are not required with mild or moderate hepatic impairment. The use has not been studied with severe hepatic impairment, thus use is not recommended in this population. Olumiant® is not recommended for use in patients with an estimated GFR of <60ml/min/1.73m^2.

Use is not recommended in patients with an absolute lymphocyte count (ALC) <500cells/mm^3, absolute neutrophil count (ANC) <1000cells/mm^3 or hemoglobin level <8g/dL. Avoid use in patients with active, serious infection, including localized infections. Dose adjustments are required for patients that develop lymphopenia, neutropenia, and anemia. Please refer to the prescribing information for specific details with dosing. If a patient develops a serious infection, hold treatment until the infection is controlled.

Drug Interactions: Use has not been studied in combination with other JAK inhibitors or with other biologic DMARDs. Baricitinib exposure is increased when co-administered with strong OAT3 inhibitors (such as probenecid), thus concomitant use is not recommended. Avoid the use of live vaccines with Olumiant®.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Olumiant® 2mg) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than placebo.* The most frequently reported adverse events included upper respiratory tract infection (4.6%), nausea (1.1%), herpes simplex (0.1%), and herpes zoster (0.6%).

Olumiant® carries a box warning regarding the increased risk of serious infections, malignancy, and thrombosis. Patients treated with Olumiant® are increased risk for developing serious infections that may lead to hospitalization or death. Most who developed these infections were taking concomitant immunosuppressants. If a serious infection develops, discontinue treatment. The risks and benefits of Olumiant® treatment should be carefully considered prior to starting treatment in patients with chronic or recurrent infection. Monitor for the development of signs and symptoms of infection during and after treatment, including the potential development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to starting treatment. In addition, lymphomas and other malignancies have been observed in patients treated with Olumiant®. (Periodic skin exams are recommended for patients who are at increased risk for skin cancer, as non-melanoma skin cancers have been reported with treatment.) Last, thrombosis, including deep venous thrombosis and pulmonary embolism, have been observed at an increased incidence in patients treated with Olumiant® compared with placebo. Patients with symptoms of thrombosis should be promptly assessed.

Laboratory abnormalities have been reported with treatment, including an increased incidence of neutropenia as compared with placebo. Assess absolute neutrophil count (ANC) at baseline and thereafter per routine patient management. Avoid starting or interrupt treatment in patients with an ANC <1000 cells/mm^3. Lymphopenia has been reported. Absolute lymphocyte count (ALC) <500 cells/mm^3 was reported in clinical trials with Olumiant®. Avoid or interrupt treatment in patients with an ALC <500cells/mm^3. Assess levels at baseline and thereafter per routine patient management. In addition, anemia was reported, with decreases in hemoglobin less to less than 8gm/ml in clinical trials. Avoid or interrupt treatment in patients with hemoglobin <8gm/dl. Assess at baseline and thereafter per routine patient management.

Liver enzyme elevations were observed in clinical trials with Olumiant® as compared with placebo. Increases ≥ 5 times and ≥10 times the upper limit of normal were seen for both ALT and AST in patients treated with Olumiant®. Assess levels at baseline and thereafter per routine patient management.

Lipid parameters were increased with Olumiant® treatment, including total cholesterol, LDL-cholesterol, and HDL-cholesterol. Assess lipid parameters about 12 weeks after starting treatment.

Gastrointestinal perforation events have been reported in clinical trials with Olumiant®. Use treatment with caution in patients at risk for GI perforation. If patients present with new onset abdominal symptoms, promptly evaluate.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Lilly

Analysis: The safety and efficacy of Olumiant® were assessed in 2 dose-ranging and 4 confirmatory phase 3 trials. The 2 confirmatory trials included in the prescribing information will be discussed below. Two phase-3 confirmatory trials included adults with moderately to severely active RA with at least 6 tender and 6 swollen joints at baseline. These trials were multicenter, randomized, double-blind placebo-controlled trials that were of 24 weeks in duration. Study III (N=684) included adults who had an inadequate response or intolerance to conventional DMARDs (cDMARD) while Study IV (N=527) included adults who had an inadequate response or intolerance to 1 or more TNF inhibitor therapies with or without other biologic DMARDs. The primary endpoint in both studies was the proportion who achieved an ACR20 response at week 12. The Disease Activity Score (DAS28-CRP) was also assessed.

Results of the clinical response can be seen in the table below, which was adopted from the prescribing information.

Treatment	cDMARD inadequate response		TNF inhibitor inadequate response	
	Study III		Study IV	
	Placebo (N=228)	Olumiant® 2mg (N=229)	Placebo (N=176)	Olumiant® 2mg (N=174)
ACR20				
Week 12	39%	66%	27%	49%
Treatment differences	27%		22%	
Week 24	42%	61%	27%	45%
Treatment differences	19%		18%	
ACR50				
Week 12	13%	34%	8%	20%
Treatment differences	21%		12%	
Week 24	21%	41%	13%	23%
Treatment differences	20%		10%	
ACR70				
Week 12	3%	18%	2%	13%
Treatment differences	15%		11%	
Week 24	8%	25%	3%	13%
Treatment differences	17%		10%	
DAS28-CRP<2.6				
Week 12	9%	26%	4%	11%
Week 24	11%	31%	6%	11%

Improvement in physical function was measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI). Adults receiving Olumiant® 2mg demonstrated greater improvement from baseline in physical functioning compared to placebo at week 24, with the mean difference from placebo being -0.24 in study III and -0.23 in study IV. In addition, general health status was assessed by the Short Form health survey (SF-36). Compared to placebo, patients in the Olumiant® group demonstrated greater improvement from baseline in the physical component summary score and the physical function, role physical, bodily pain, vitality, and general health domains at week 12, but with no consistent improvements in the mental component summary scores or the emotional, mental health, and social functioning domains.

Place in Therapy: Olumiant® is the second oral FDA approved Janus kinase inhibitor (JAK) and is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies. Use in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), or with potent immunosuppressants is not recommended. It was found to be significantly effective as compared with placebo for the primary endpoint of the proportion who achieved an ACR20 response at week 12.

A 2017 double-blind, placebo- and active-controlled phase 3 study in the NEJM by Taylor et al[2] suggested that baricitinib 4mg was significantly more effective as compared with placebo for the primary endpoint of the proportion achieving an ACR20 response at week 12 (70% vs 40%, respectively; p<0.001). In addition, baricitinib 4mg was found to be non-inferior to adalimumab at week 12 for ACR response and per the statistical analysis plan, baricitinib was considered to be significantly superior to adalimumab (70% vs 61%, respectively; p=0.014).

In one clinical trial of patients with RA, the 4 mg/day dose of Olumiant® was associated with significant clinical improvement compared to adalimumab. The FDA, however, approved only the 2 mg/day dose due to concerns about the risk of thrombotic events seen with the higher dose. There is no evidence to support that the approved 2 mg/day dose of Olumiant® is safer or more effective than the other currently available, more cost-effective medications. It is therefore recommended that Olumiant® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Olumiant [package insert]. Indianapolis, IN: Lilly USA; 2018.
[2] Taylor PC, Keystone EC, van der Helide D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. NEJM. 2017; 376(7): 652-662.