

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207924Orig1s000**

**LABELING**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use OLUMIANT safely and effectively. See full prescribing information for OLUMIANT.

OLUMIANT (baricitinib) tablets, for oral use  
Initial U.S. Approval: 2018

**WARNING: SERIOUS INFECTIONS, MALIGNANCY, AND THROMBOSIS**

See full prescribing information for complete boxed warning.

- Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving OLUMIANT. (5.1)
- If a serious infection develops, interrupt OLUMIANT until the infection is controlled. (5.1)
- Prior to starting OLUMIANT, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting OLUMIANT. (5.1)
- Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)
- Lymphoma and other malignancies have been observed in patients treated with OLUMIANT. (5.2)
- Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, some fatal, have occurred in patients treated with OLUMIANT. Patients with symptoms of thrombosis should be evaluated promptly. (5.3)

**INDICATIONS AND USAGE**

OLUMIANT® is a Janus kinase (JAK) inh bitor indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies. (1.1)

Limitation of Use: Use of OLUMIANT in combination with other JAK inh bitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1.1)

**DOSAGE AND ADMINISTRATION**

The recommended dose of OLUMIANT is 2 mg once daily. (2.1)  
OLUMIANT may be used as monotherapy or in combination with methotrexate or other DMARDs. (2.1)

**Anemia:** Avoid initiation or interrupt OLUMIANT in patients with hemoglobin less than 8 g/dL. (2.2, 2.3, 5.5)

**Lymphopenia:** Avoid initiation or interrupt OLUMIANT in patients with an Absolute Lymphocyte Count less than 500 cells/mm<sup>3</sup>. (2.2, 2.3, 5.5)

**Neutropenia:** Avoid initiation or interrupt OLUMIANT in patients with an Absolute Neutrophil Count less than 1000 cells/mm<sup>3</sup>. (2.2, 2.3, 5.5)

**DOSAGE FORMS AND STRENGTHS**

Tablets (not scored): 2 mg (3)

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

- **Serious Infections:** Avoid use of OLUMIANT in patients with active, serious infection, including localized infections. If a serious infection develops, interrupt OLUMIANT therapy until the infection is controlled. Do not give OLUMIANT to patients with active tuberculosis. (5.1)
- **Thrombosis:** Use with caution in patients who may be at increased risk. (5.3)
- **Gastrointestinal Perforations:** Use with caution in patients who may be at increased risk. (5.4)
- **Laboratory Assessment:** Recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids. (5.5)
- **Vaccinations:** Avoid use of OLUMIANT with live vaccines. (5.6)

**ADVERSE REACTIONS**

Adverse reactions (greater than or equal to 1%) include: upper respiratory tract infections, nausea, herpes simplex, and herpes zoster. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**DRUG INTERACTIONS**

OLUMIANT is not recommended in patients taking strong Organic Anion Transporter 3 (OAT3) inhibitors (e.g., probenecid). (2.5, 7.1)

**USE IN SPECIFIC POPULATIONS**

- **Hepatic Impairment:** OLUMIANT is not recommended in patients with severe hepatic impairment. (2.4, 8.6)
- **Renal Impairment:** OLUMIANT is not recommended in patients with moderate or severe renal impairment. (2.4, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 05/2018

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## FULL PRESCRIBING INFORMATION

### WARNING: SERIOUS INFECTIONS, MALIGNANCY, AND THROMBOSIS

#### SERIOUS INFECTIONS

Patients treated with OLUMIANT are at risk for developing serious infections that may lead to hospitalization or death [see *Warnings and Precautions (5.1) and Adverse Reactions (6.1)*]. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt OLUMIANT until the infection is controlled.

Reported infections include:

- Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before initiating OLUMIANT and during therapy. Treatment for latent infection should be considered prior to OLUMIANT use.
- Invasive fungal infections, including candidiasis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.
- Bacterial, viral, and other infections due to opportunistic pathogens.

The risks and benefits of treatment with OLUMIANT should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with OLUMIANT including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy [see *Warnings and Precautions (5.1)*].

#### MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with OLUMIANT [see *Warnings and Precautions (5.2)*].

#### THROMBOSIS

Thrombosis, including deep venous thrombosis and pulmonary embolism, has been observed at an increased incidence in patients treated with OLUMIANT compared to placebo. In addition, there were cases of arterial thrombosis. Many of these adverse events were serious and some resulted in death. Patients with symptoms of thrombosis should be promptly evaluated. [See *Warnings and Precautions (5.3)*].

## 1 INDICATIONS AND USAGE

### 1.1 Rheumatoid Arthritis

OLUMIANT® (baricitinib) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies.

Limitation of Use: Use of OLUMIANT in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosage in Rheumatoid Arthritis

The recommended dose of OLUMIANT is 2 mg once daily.

OLUMIANT may be used as monotherapy or in combination with methotrexate or other DMARDs.

OLUMIANT is given orally with or without food [see *Clinical Pharmacology (12.3)*].

### 2.2 General Considerations for Administration

- OLUMIANT initiation is not recommended in patients with an absolute lymphocyte count (ALC) less than 500 cells/mm<sup>3</sup>, absolute neutrophil count (ANC) less than 1000 cells/mm<sup>3</sup>, or hemoglobin level less than 8 g/dL [see *Warnings and Precautions (5.5)*].
- Avoid use of OLUMIANT in patients with active, serious infection, including localized infections [see *Warnings and Precautions (5.1)*].

Prior to initiating OLUMIANT, test patients for latent tuberculosis (TB). If positive, consider treating for TB prior to OLUMIANT use [see *Warnings and Precautions (5.1)*].

### 2.3 Dose Modifications Due to Serious Infections and Cytopenias

If a patient develops a serious infection, hold treatment with OLUMIANT until the infection is controlled.

Modify dosage in cases of lymphopenia, neutropenia or anemia (Tables 1, 2, and 3). For treatment initiation criteria [see *Dosage and Administration (2.2)*].

**Table 1: Dose Adjustments for Lymphopenia**

Low Absolute Lymphocyte Count (ALC)	
Lab Value (cells/mm <sup>3</sup> )	Recommendation
ALC greater than or equal to 500	Maintain dose
ALC less than 500	Interrupt OLUMIANT until ALC greater than or equal to 500

**Table 2: Dose Adjustments for Neutropenia**

Low Absolute Neutrophil Count (ANC)	
Lab Value (cells/mm <sup>3</sup> )	Recommendation
ANC greater than or equal to 1000	Maintain dose
ANC less than 1000	Interrupt OLUMIANT until ANC greater than or equal to 1000

**Table 3: Dose Adjustments for Anemia**

Low Hemoglobin Value	
Lab Value (g/dL)	Recommendation
Greater than or equal to 8	Maintain dose
Less than 8	Interrupt OLUMIANT until hemoglobin greater than or equal to 8

**2.4 Dose Modifications in Patients with Renal or Hepatic Impairment**

- OLUMIANT is not recommended for use in patients with estimated GFR of less than 60 mL/min/1.73 m<sup>2</sup> [see *Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)*].
- OLUMIANT is not recommended for use in patients with severe hepatic impairment.

**2.5 Dose Modifications Due to Drug Interactions**

OLUMIANT is not recommended for use in patients taking strong Organic Anion Transporter 3 (OAT3) inhibitors, such as probenecid [see *Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

**3 DOSAGE FORMS AND STRENGTHS**

OLUMIANT for oral administration is available as debossed, film-coated, immediate-release tablets:

- 2 mg tablet contains a recessed area on each face of the tablet surface, is light pink, oblong, debossed with "Lilly" on one side and "2" on the other.

**4 CONTRAINDICATIONS**

None.

**5 WARNINGS AND PRECAUTIONS****5.1 Serious Infections**

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in rheumatoid arthritis patients receiving OLUMIANT. The most common serious infections reported with OLUMIANT included pneumonia, herpes zoster, and urinary tract infection [see *Adverse Reactions (6.1)*]. Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, esophageal candidiasis, pneumocystosis, acute histoplasmosis, cryptococcosis, cytomegalovirus, and BK virus were reported with OLUMIANT. Some patients have presented with disseminated rather than localized disease, and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Avoid use of OLUMIANT in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating OLUMIANT in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with OLUMIANT. Interrupt OLUMIANT if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with OLUMIANT should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and OLUMIANT should be interrupted if the patient is not responding to therapy. Do not resume OLUMIANT until the infection is controlled.

### Tuberculosis

Evaluate and test patients for latent or active infection prior to administration of OLUMIANT. Patients with latent tuberculosis (TB) should be treated with standard antimycobacterial therapy before initiating OLUMIANT.

OLUMIANT should not be given to patients with active TB. Consider anti-TB therapy prior to initiation of OLUMIANT in patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but who have risk factors for TB infection. Consultation with a physician with expertise in the treatment of TB is recommended to aid in the decision about whether initiating anti-TB therapy is appropriate for an individual patient.

Monitor patients for the development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating therapy.

### Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical studies with OLUMIANT. If a patient develops herpes zoster, interrupt OLUMIANT treatment until the episode resolves.

The impact of OLUMIANT on chronic viral hepatitis reactivation is unknown. Patients with evidence of active hepatitis B or C infection were excluded from clinical trials. Patients who were positive for hepatitis C antibody but negative for hepatitis C virus RNA were permitted to enroll. Patients with positive hepatitis B surface antibody and hepatitis B core antibody, without hepatitis B surface antigen, were permitted to enroll; such patients should be monitored for expression of hepatitis B virus (HBV) DNA. Should HBV DNA be detected, consult with a hepatologist. Perform screening for viral hepatitis in accordance with clinical guidelines before starting therapy with OLUMIANT.

## **5.2 Malignancy and Lymphoproliferative Disorders**

Consider the risks and benefits of OLUMIANT treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing OLUMIANT in patients who develop a malignancy. Malignancies were observed in clinical studies of OLUMIANT [see *Adverse Reactions (6.1)*].

### Non-melanoma skin cancers

Non-melanoma skin cancers (NMSCs) have been reported in patients treated with OLUMIANT. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

## **5.3 Thrombosis**

Thrombosis, including deep venous thrombosis (DVT) and pulmonary embolism (PE), has been observed at an increased incidence in patients treated with OLUMIANT compared to placebo. In addition, arterial thrombosis events in the extremities have been reported in clinical studies with OLUMIANT. Many of these adverse events were serious and some resulted in death. There was no clear relationship between platelet count elevations and thrombotic events. OLUMIANT should be used with caution in patients who may be at increased risk of thrombosis. If clinical features of DVT/PE or arterial thrombosis occur, patients should be evaluated promptly and treated appropriately.

## **5.4 Gastrointestinal Perforations**

Events of gastrointestinal perforation have been reported in clinical studies with OLUMIANT, although the role of JAK inhibition in these events is not known.

OLUMIANT should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

## **5.5 Laboratory Abnormalities**

Neutropenia – Treatment with OLUMIANT was associated with an increased incidence of neutropenia (ANC less than 1000 cells/mm<sup>3</sup>) compared to placebo. Avoid initiation or interrupt OLUMIANT treatment in patients with an ANC less than 1000 cells/mm<sup>3</sup>. Evaluate at baseline and thereafter according to routine patient management. For recommended modifications based on ANC [see *Dosage and Administration (2.3)* and *Adverse Reactions (6.1)*].

Lymphopenia – ALC less than 500 cells/mm<sup>3</sup> were reported in OLUMIANT clinical trials. Lymphocyte counts less than the lower limit of normal were associated with infection in patients treated with OLUMIANT, but not placebo.

Avoid initiation or interrupt OLUMIANT treatment in patients with an ALC less than 500 cells/mm<sup>3</sup>. Evaluate at baseline and thereafter according to routine patient management. For recommended modifications based on ALC results [see *Dosage and Administration (2.3)*].

Anemia – Decreases in hemoglobin levels to less than 8 g/dL were reported in OLUMIANT clinical trials. Avoid initiation or interrupt OLUMIANT treatment in patients with hemoglobin less than 8 g/dL. Evaluate at baseline and thereafter according to routine patient management. For recommended modifications based on hemoglobin results [see *Dosage and Administration (2.3)*].

Liver Enzyme Elevations – Treatment with OLUMIANT was associated with increased incidence of liver enzyme elevation compared to placebo. Increases to greater than or equal to 5x and greater than or equal to 10x upper limit of normal (ULN) were observed for both ALT and AST in patients in OLUMIANT clinical trials.

Evaluate at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. If increases in ALT or AST

are observed and drug-induced liver injury is suspected, interrupt OLUMIANT until this diagnosis is excluded [see *Adverse Reactions (6.1)*].

**Lipid Elevations** – Treatment with OLUMIANT was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Assessment of lipid parameters should be performed approximately 12 weeks following OLUMIANT initiation [see *Adverse Reactions (6.1)*].

Manage patients according to clinical guidelines for the management of hyperlipidemia.

## 5.6 Vaccinations

Avoid use of live vaccines with OLUMIANT.

Update immunizations in agreement with current immunization guidelines prior to initiating OLUMIANT therapy.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

The following data include six randomized double-blind placebo-controlled studies (three Phase 2, three Phase 3) and a long-term extension study. All patients had moderately to severely active RA. Patients were randomized to placebo (1070 patients), OLUMIANT 2 mg (479 patients), or baricitinib 4 mg (997 patients).

Patients could be switched to baricitinib 4 mg from placebo or OLUMIANT 2 mg from as early as Week 12 depending on the study design. All patients initially randomized to placebo were switched to baricitinib 4 mg by Week 24.

During the 16-week treatment period, adverse events leading to discontinuation of treatment were reported by 35 patients (11.4 events per 100 patient-years) treated with placebo, 17 patients (12.1 events per 100 patient-years) with OLUMIANT 2 mg, and 40 patients (13.4 events per 100 patient-years) treated with baricitinib 4 mg.

During 0 to 52 week exposure, adverse events leading to discontinuation of treatment were reported by 31 patients (9.2 events per 100 patient-years) with OLUMIANT 2 mg, and 92 patients (10.2 events per 100 patient-years) treated with baricitinib 4 mg.

**Overall Infections** – During the 16-week treatment period, infections were reported by 253 patients (82.1 events per 100 patient-years) treated with placebo, 139 patients (99.1 events per 100 patient-years) treated with OLUMIANT 2 mg, and 298 patients (100.1 events per 100 patient-years) treated with baricitinib 4 mg.

During 0 to 52 week exposure, infections were reported by 200 patients (59.6 events per 100 patient-years) treated with OLUMIANT 2 mg, and 500 patients (55.3 events per 100 patient-years) treated with baricitinib 4 mg.

In the 0 to 52 week exposure population, the most commonly reported infections with OLUMIANT were viral upper respiratory tract infection, upper respiratory tract infection, urinary tract infection, and bronchitis.

**Serious Infections** – During the 16-week treatment period, serious infections were reported in 13 patients (4.2 events per 100 patient-years) treated with placebo, 5 patients (3.6 events per 100 patient-years) treated with OLUMIANT 2 mg, and 11 patients (3.7 events per 100 patient-years) treated with baricitinib 4 mg.

During 0 to 52 week exposure, serious infections were reported in 14 patients (4.2 events per 100 patient-years) treated with OLUMIANT 2 mg and 32 patients (3.5 events per 100 patient-years) treated with baricitinib 4 mg.

In the 0 to 52 week exposure population, the most commonly reported serious infections with OLUMIANT were pneumonia, herpes zoster, and urinary tract infection [see *Warnings and Precautions (5.1)*].

**Tuberculosis** – During the 16-week treatment period, no events of tuberculosis were reported.

During 0 to 52 week exposure, events of tuberculosis were reported in 0 patients treated with OLUMIANT 2 mg and 1 patient (0.1 per 100 patient-years) treated with baricitinib 4 mg [see *Warnings and Precautions (5.1)*].

Cases of disseminated tuberculosis were also reported.

**Opportunistic Infections (excluding tuberculosis)** – During the 16-week treatment period, opportunistic infections were reported in 2 patients (0.6 per 100 patient-years) treated with placebo, 0 patients treated with OLUMIANT 2 mg and 2 patients (0.7 per 100 patient-years) treated with baricitinib 4 mg.

During 0 to 52 week exposure, opportunistic infections were reported in 1 patient (0.3 per 100 patient-years) treated with OLUMIANT 2 mg and 5 patients (0.6 per 100 patient-years) treated with baricitinib 4 mg [see *Warnings and Precautions (5.1)*].

**Malignancy** – During the 16-week treatment period, malignancies excluding non-melanoma skin cancers (NMSC) were reported in 0 patients treated with placebo, 1 patient (0.7 per 100 patient-years) treated with OLUMIANT 2 mg, and 1 patient (0.3 per 100 patient-years) treated with baricitinib 4 mg.

During the 0 to 52 week treatment period, malignancies excluding NMSC were reported in 2 patients (0.6 per 100 patient-years) treated with OLUMIANT 2 mg and 6 patients (0.7 per 100 patient-years) treated with baricitinib 4 mg [see *Warnings and Precautions (5.2)*].

**Venous Thrombosis** – During the 16-week treatment period, venous thromboses (deep vein thrombosis or pulmonary embolism) were reported in 0 patients treated with placebo, 0 patients treated with OLUMIANT 2 mg, and 5 patients (1.7 per 100 patient-years) treated with baricitinib 4 mg.

During the 0 to 52 week treatment period, venous thromboses were reported in 2 patients (0.6 per 100 patient-years) treated with OLUMIANT 2 mg and 7 patients (0.8 per 100 patient-years) treated with baricitinib 4 mg.

**Arterial Thrombosis** – During the 16-week treatment period, arterial thromboses were reported in 1 patient treated with placebo (0.3 per 100 patient-years), 2 patients (1.4 per 100 patient-years) treated with OLUMIANT 2 mg, and 2 patients (0.7 per 100 patient-years) treated with baricitinib 4 mg.

During the 0 to 52 week treatment period, arterial thromboses were reported in 3 patients (0.9 per 100 patient-years) treated with OLUMIANT 2 mg and 3 patients (0.3 per 100 patient-years) treated with baricitinib 4 mg.

#### **Laboratory Abnormalities**

**Neutropenia** – During the 16-week treatment period, neutrophil counts below 1000 cells/mm<sup>3</sup> occurred in 0% of patients treated with placebo, 0.6% of patients treated with OLUMIANT 2 mg, and 0.3% of patients treated with baricitinib 4 mg. There were no neutrophil counts below 500 cells/mm<sup>3</sup> observed in any treatment group [see *Warnings and Precautions* (5.1, 5.5)].

**Platelet Elevations** – During the 16-week treatment period, increases in platelet counts above 600,000 cells/mm<sup>3</sup> occurred in 1.1% of patients treated with placebo, 1.1% of patients treated with OLUMIANT 2 mg, and 2.0% of patients treated with baricitinib 4 mg. Mean platelet count increased by 3000 cells/mm<sup>3</sup> at 16 weeks in patients treated with placebo, by 15,000 cells/mm<sup>3</sup> at 16 weeks in patients treated with OLUMIANT 2 mg and by 23,000 cells/mm<sup>3</sup> in patients treated with baricitinib 4 mg.

**Liver Enzyme Elevations** – Events of increases in liver enzymes greater than or equal to 3x ULN were observed in patients treated with OLUMIANT [see *Warnings and Precautions* (5.5)].

- During the 16-week treatment period, ALT elevations greater than or equal to 3x ULN occurred in 1.0% of patients treated with placebo, 1.7% of patients treated with OLUMIANT 2 mg, and 1.4% of patients treated with baricitinib 4 mg.
- During the 16-week treatment period, AST elevations greater than or equal to 3x ULN occurred in 0.8% of patients treated with placebo, 1.3% of patients treated with OLUMIANT 2 mg, and 0.8% of patients treated with baricitinib 4 mg.
- In a phase 3 study of DMARD naive patients, during the 24-week treatment period, ALT and AST elevations  $\geq 3x$  ULN occurred in 1.9% and 0% of patients treated with methotrexate monotherapy, 1.9% and 1.3% of patients treated with baricitinib 4 mg monotherapy, and 4.7% and 1.9% of patients treated with baricitinib 4 mg plus methotrexate.

**Lipid Elevations** – In controlled clinical trials, OLUMIANT treatment was associated with dose-related increases in lipid parameters including total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol. Elevations were observed at 12 weeks and remained stable thereafter. During the 12-week treatment period, changes in lipid parameters are summarized below:

- Mean LDL cholesterol increased by 8 mg/dL in patients treated with OLUMIANT 2 mg and by 14 mg/dL in patients treated with baricitinib 4 mg.
- Mean HDL cholesterol increased by 7 mg/dL in patients treated with OLUMIANT 2 mg and by 9 mg/dL in patients treated with baricitinib 4 mg.
- The mean LDL/HDL ratio remained stable.
- Mean triglycerides increased by 7 mg/dL in patients treated with OLUMIANT 2 mg and by 15 mg/dL in patients treated with baricitinib 4 mg.

[See *Warnings and Precautions* (5.5)].

**Creatine Phosphokinase (CPK)** – OLUMIANT treatment was associated with increases in CPK within one week of starting OLUMIANT and plateauing after 8 to 12 weeks. At 16 weeks, the mean change in CPK for OLUMIANT 2 mg and baricitinib 4 mg was 37 IU/L and 52 IU/L, respectively.

**Creatinine** – In controlled clinical trials, dose-related increases in serum creatinine were observed with OLUMIANT treatment. At 52 weeks, the mean increase in serum creatinine was less than 0.1 mg/dL with baricitinib 4 mg. The clinical significance of the observed serum creatinine increases is unknown.

#### **Other Adverse Reactions**

Other adverse reactions are summarized in Table 4.



**Table 4: Adverse Reactions occurring in greater than or equal to 1% of OLUMIANT 2 mg and Baricitinib 4 mg Treated Patients in Placebo-Controlled Trials**

	Weeks 0-16		
	Placebo n=1070 (%)	OLUMIANT 2 mg n=479 (%)	Baricitinib 4 mg n=997 (%)
<b>Events</b>			
Upper respiratory tract infections <sup>a</sup>	11.7	16.3	14.7
Nausea	1.6	2.7	2.8
Herpes simplex <sup>b</sup>	0.7	0.8	1.8
Herpes zoster	0.4	1.0	1.4

<sup>a</sup> Includes acute sinusitis, acute tonsillitis, chronic tonsillitis, epiglottitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinobronchitis, sinusitis, tonsillitis, tracheitis, and upper respiratory tract infection.

<sup>b</sup> Includes eczema herpeticum, genital herpes, herpes simplex, ophthalmic herpes simplex, and oral herpes.

Additional adverse drug reactions occurring in fewer than 1% of patients: acne.

## 7 DRUG INTERACTIONS

### 7.1 Strong OAT3 Inhibitors

Baricitinib exposure is increased when OLUMIANT is co-administered with strong OAT3 inhibitors (such as probenecid) [see *Dosage and Administration (2.5)* and *Clinical Pharmacology (12.3)*].

### 7.2 Other JAK Inhibitors or Biologic DMARDs

OLUMIANT has not been studied in combination with other JAK inhibitors or with biologic DMARDs [see *Indications and Usage (1.1)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

The limited human data on use of OLUMIANT in pregnant women are not sufficient to inform a drug-associated risk for major birth defects or miscarriage. In animal embryo-fetal development studies, oral baricitinib administration 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 embryoletality (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 [see *Animal Data*].

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

#### Data

##### Animal Data

In an embryofetal development study in pregnant rats, dosed orally during the period of organogenesis from gestation days 6 to 17, baricitinib was teratogenic (skeletal malformations that consisted of bent limb bones and rib anomalies) at exposures equal to or greater than approximately 20 times the MRHD (on an AUC basis at maternal oral doses of 10 mg/kg/day and higher). No developmental toxicity was observed in rats at an exposure approximately 5 times the MRHD (on an AUC basis at a maternal oral dose of 2 mg/kg/day).

In an embryofetal development study in pregnant rabbits, dosed orally during the period of organogenesis from gestation days 7 to 20, embryoletality, decreased fetal body weights, and skeletal malformations (rib anomalies) were observed in the presence of maternal toxicity at an exposure approximately 84 times the MRHD (on an AUC basis at a maternal oral dose of 30 mg/kg/day). Embryoletality consisted of increased post-implantation loss that was due to elevated incidences of both early and late resorptions. No developmental toxicity was observed in rabbits at an exposure approximately 12 times the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

In a pre- and post-natal development study in pregnant female rats dosed orally from gestation day 6 through lactation day 20, adverse findings observed in pups included decreased survival from birth to post-natal day 4 (due to increased stillbirths and early neonatal deaths), decreased birth weight, decreased body weight gain during the pre-weaning phase, increased incidence of malrotated forelimbs during the pre-weaning phase, and decreased cytotoxic T cells on PND 35 with recovery by PND 65 at exposures approximately 43 times the MRHD (on an AUC basis at a maternal oral dose of 25 mg/kg/day). Developmental delays (that may be secondary to decreased body weight gain) were observed in males and females at exposures approximately 43 times the MRHD (on an AUC basis at a maternal oral dose of 25 mg/kg/day). These findings included decreased forelimb and hindlimb grip strengths, and delayed mean age of sexual maturity. No developmental toxicity was observed in rats at an exposure approximately 9 times the MRHD (on an AUC basis at a maternal oral dose of 5 mg/kg/day).

## 8.2 Lactation

### Risk Summary

No information is available on the presence of OLUMIANT in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Baricitinib is present in the milk of lactating rats. Due to species-specific differences in lactation physiology, the clinical relevance of these data are not clear. Because of the potential for serious adverse reactions in nursing infants, advise an OLUMIANT-treated woman not to breastfeed.

### Data

A single oral dose of 25 mg/kg radiolabeled baricitinib was administered to lactating female Sprague-Dawley rats on post-partum day 13. Drug exposure was approximately 45-fold greater in milk than in plasma based on AUC<sub>0-1</sub> values.

## 8.4 Pediatric Use

The safety and effectiveness of OLUMIANT in pediatric patients have not been established.

## 8.5 Geriatric Use

Of the 3100 patients treated in the four phase 3 studies, a total of 537 rheumatoid arthritis patients were 65 years of age and older, including 71 patients 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out [see *Clinical Pharmacology* (12.3)].

OLUMIANT is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. [See *Dosing and Administration* (2.4)].

## 8.6 Hepatic Impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment. The use of OLUMIANT has not been studied in patients with severe hepatic impairment and is therefore not recommended [see *Dosage and Administration* (2.4) and *Clinical Pharmacology* (12.3)].

## 8.7 Renal Impairment

Renal function was found to significantly affect baricitinib exposure. OLUMIANT is not recommended for use in patients with estimated GFR of less than 60 mL/min/1.73 m<sup>2</sup> [see *Dosage and Administration* (2.4) and *Clinical Pharmacology* (12.3)].

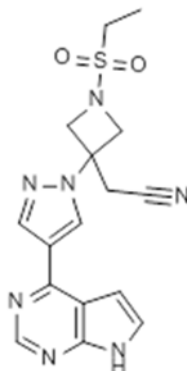
## 10 OVERDOSAGE

Single doses up to 40 mg and multiple doses of up to 20 mg daily for 10 days have been administered in clinical trials without dose-limiting toxicity. Pharmacokinetic data of a single dose of 40 mg in healthy volunteers indicate that more than 90% of the administered dose is expected to be eliminated within 24 hours.

In case of an overdose, it is recommended that the patient should be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

## 11 DESCRIPTION

OLUMIANT (baricitinib) is a Janus kinase (JAK) inhibitor with the chemical name {1-(ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile. Baricitinib has an empirical formula of C<sub>16</sub>H<sub>17</sub>N<sub>7</sub>O<sub>2</sub>S and a molecular weight of 371.42. Baricitinib has the following structural formula:



OLUMIANT tablets contain a recessed area on each face of the tablet surface and are available for oral administration as debossed, film-coated, immediate-release tablets. The 2 mg tablet is light pink, oblong, debossed with “Lilly” on one side and “2” on the other.

Each tablet contains 2 mg of baricitinib and the following inactive ingredients: croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, ferric oxide, lecithin (soya), polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 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. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Baricitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs.

JAK enzymes transmit cytokine signaling through their pairing (e.g., JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/JAK2, JAK2/TYK2). In cell-free isolated enzyme assays, baricitinib had greater inhibitory potency at JAK1, JAK2 and TYK2 relative to JAK3. In human leukocytes, baricitinib inhibited cytokine induced STAT phosphorylation mediated by JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, or JAK2/TYK2 with comparable potencies. However, the relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known.

### 12.2 Pharmacodynamics

Baricitinib inhibition of IL-6 induced STAT3 phosphorylation – Baricitinib administration resulted in a dose dependent inhibition of IL-6 induced STAT3 phosphorylation in whole blood from healthy subjects with maximal inhibition observed approximately 1 hour after dosing, which returned to near baseline by 24 hours. Similar levels of inhibition were observed using either IL-6 or TPO as the stimulus.

Immunoglobulins – Mean serum IgG, IgM, and IgA values decreased by 12 weeks after starting treatment with OLUMIANT, and remained stable through at least 52 weeks. For most patients, changes in immunoglobulins occurred within the normal reference range.

C-reactive protein – In patients with rheumatoid arthritis, decreases in serum C-reactive protein (CRP) were observed as early as one week after starting treatment with OLUMIANT and were maintained throughout dosing.

Cardiac Electrophysiology – At a dose 10 times the maximum recommended dose, baricitinib does not prolong the QT interval to any clinically relevant extent.

### 12.3 Pharmacokinetics

Following oral administration of OLUMIANT, peak plasma concentrations are reached approximately at 1 hour. A dose-proportional increase in systemic exposure was observed in the therapeutic dose range. The pharmacokinetics of baricitinib do not change over time. Steady-state concentrations are achieved in 2 to 3 days with minimal accumulation after once-daily administration.

Absorption – The absolute bioavailability of baricitinib is approximately 80%. An assessment of food effects in healthy subjects showed that a high-fat meal decreased the mean AUC and  $C_{max}$  of baricitinib by approximately 11% and 18%, respectively, and delayed the  $t_{max}$  by 0.5 hours. Administration with meals is not associated with a clinically relevant effect on exposure. In clinical studies, OLUMIANT was administered without regard to meals.

Distribution – After intravenous administration, the volume of distribution is 76 L, indicating distribution of baricitinib into tissues. Baricitinib is approximately 50% bound to plasma proteins and 45% bound to serum proteins. Baricitinib is a substrate of the Pgp, BCRP, OAT3 and MATE2-K transporters, which play roles in drug distribution.

Elimination – The total body clearance of baricitinib is 8.9 L/h in patients with RA. Elimination half-life in patients with rheumatoid arthritis is approximately 12 hours.

**Metabolism** – Approximately 6% of the orally administered baricitinib dose is identified as metabolites (three from urine and one from feces), with CYP3A4 identified as the main metabolizing enzyme. No metabolites of baricitinib were quantifiable in plasma.

**Excretion** – Renal elimination is the principal clearance mechanism for baricitinib through filtration and active secretion as baricitinib is identified as a substrate of OAT3, Pgp, BCRP and MATE2-K from *in vitro* studies. In a clinical pharmacology study, approximately 75% of the administered dose was eliminated in the urine, while about 20% of the dose was eliminated in the feces. Baricitinib was excreted predominately as unchanged drug in urine (69%) and feces (15%).

### Specific Populations

#### Effects of Body Weight, Gender, Race, and Age

Body weight, gender, race, ethnicity, and age did not have a clinically relevant effect on the PK (AUC and  $C_{max}$ ) of baricitinib (Figure 1). The mean effects of intrinsic factors on PK parameters (AUC and  $C_{max}$ ) were generally within the inter-subject PK variability of baricitinib. The inter-subject variabilities (% coefficients of variation) in AUC and  $C_{max}$  of baricitinib are approximately 41% and 22%, respectively. [See *Use in Specific Populations (8.5)*].

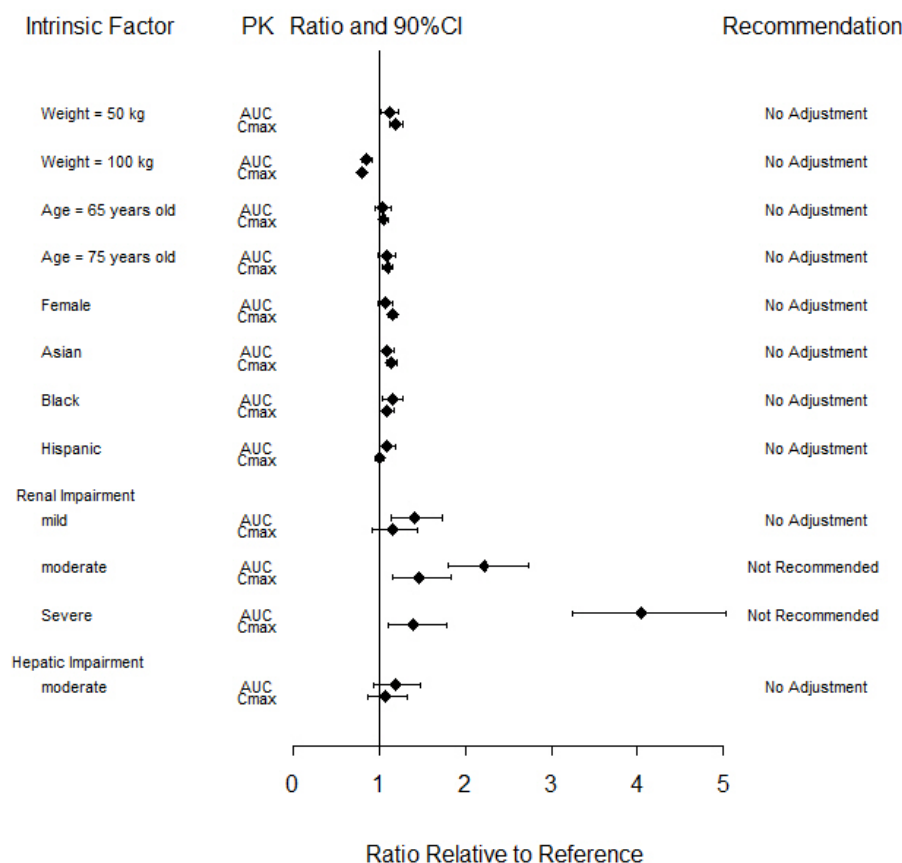
#### Renal Impairment

Baricitinib systemic exposure in AUC was increased by 1.41-, 2.22-, 4.05- and 2.41-fold for mild, moderate, severe, and ESRD (with hemodialysis) renal impairment sub-groups, respectively, compared to subjects with normal renal function. The corresponding values for increase in  $C_{max}$  were 1.16-, 1.46-, 1.40- and 0.88-fold, respectively (Figure 1) [see *Use in Specific Populations (8.7)*].

#### Hepatic Impairment

Baricitinib systemic exposure and  $C_{max}$  increased by 1.19- and 1.08-fold for the moderate hepatic impairment group, respectively, compared to subjects with normal hepatic function (Figure 1) [see *Use in Specific Populations (8.6)*].

**Figure 1: Impact of Intrinsic Factors on Baricitinib Pharmacokinetics<sup>a,b</sup>**



<sup>a</sup> Reference values for weight, age, gender, and race comparisons are 70 kg, 54 years, male, and white, respectively; reference groups for renal and hepatic impairment are subjects with normal renal and hepatic function, respectively.

<sup>b</sup> Effects of renal and hepatic impairment on baricitinib exposure were summarized from dedicated renal and hepatic impairment studies, respectively. Effects of other intrinsic factors on baricitinib exposure were summarized from population PK analysis.

## Drug Interactions

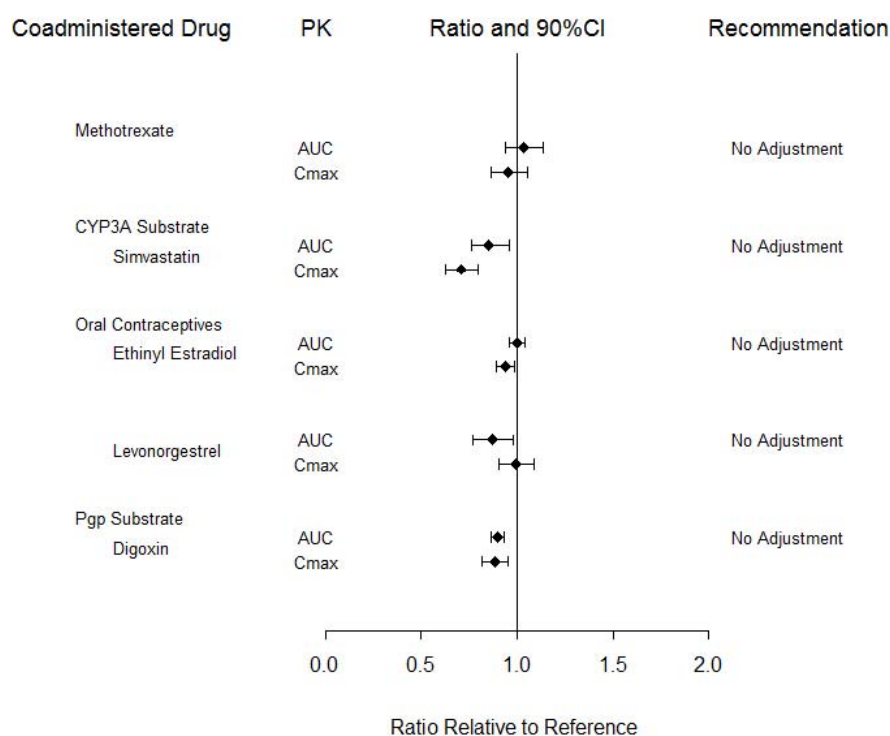
### Potential for Baricitinib to Influence the PK of Other Drugs

*In vitro*, baricitinib did not significantly inhibit or induce the activity of cytochrome P450 enzymes (CYPs 3A, 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6). In clinical pharmacology studies, there were no clinically meaningful changes in the pharmacokinetics (PK) of simvastatin, ethinyl estradiol, or levonorgestrel (CYP3A substrates) when co-administered with baricitinib.

*In vitro* studies suggest that baricitinib is not an inhibitor of the transporters, P-glycoprotein (Pgp) or Organic Anion Transporting Polypeptide (OATP) 1B1. *In vitro* data indicate baricitinib does inhibit organic anionic transporter (OAT) 1, OAT2, OAT3, organic cationic transporter (OCT) 1, OCT2, OATP1B3, Breast Cancer Resistance Protein (BCRP) and Multidrug and Toxic Extrusion Protein (MATE) 1 and MATE2-K, but clinically meaningful changes in the pharmacokinetics of drugs that are substrates for these transporters are unlikely. In clinical pharmacology studies there were no clinically meaningful effects on the PK of digoxin (Pgp substrate) or methotrexate (substrate of several transporters) when co-administered with baricitinib.

Exposure changes of drugs following co-administration with baricitinib are shown in Figure 2.

**Figure 2: Impact of Baricitinib on the Pharmacokinetics of Other Drugs<sup>a</sup>**



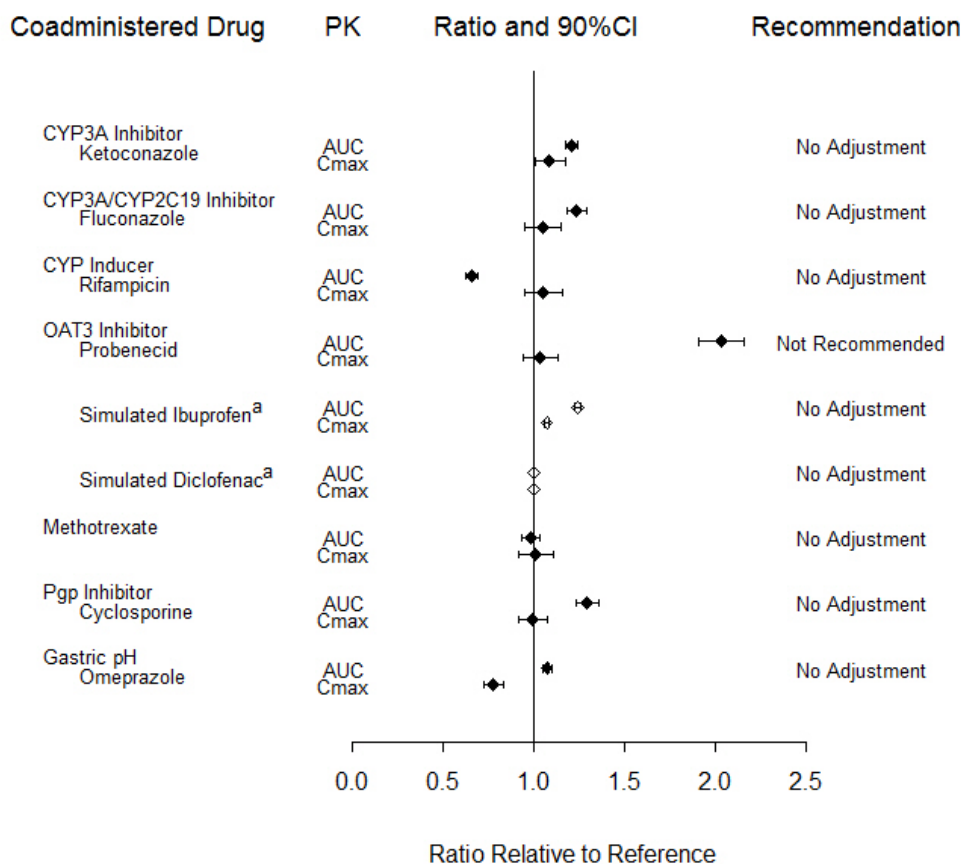
<sup>a</sup> Reference group is administration of concomitant drug alone.

### Potential for Other Drugs to Influence the PK of Baricitinib

*In vitro* studies suggest that baricitinib is a CYP3A4 substrate. In clinical pharmacology studies there was no effect on the PK of baricitinib when co-administered with ketoconazole (CYP3A inhibitor). There were no clinically meaningful changes in the PK of baricitinib when co-administered with fluconazole (CYP3A/CYP2C19/CYP2C9 inhibitor) or rifampicin (CYP3A inducer).

*In vitro* studies suggest that baricitinib is a substrate for OAT3, Pgp, BCRP and MATE2-K. In a clinical study, probenecid administration (strong OAT3 inhibitor) resulted in an approximately 2-fold increase in baricitinib AUC<sub>0-∞</sub> with no effect on C<sub>max</sub> and t<sub>max</sub> [see *Dosage and Administration (2.5)* and *Drug Interactions (7.1)*]. However, simulations with diclofenac and ibuprofen (OAT3 inhibitors with less inhibition potential) predicted minimal effect on the PK of baricitinib. In clinical pharmacology studies there was no clinically meaningful effect on the PK of baricitinib when co-administered with cyclosporine (Pgp and BCRP inhibitor). Co-administration with methotrexate (substrate of several transporters) did not have a clinically meaningful effect on the PK of baricitinib.

Exposure changes of baricitinib following co-administration with CYP inhibitors or inducers, transporter inhibitors, as well as methotrexate and the proton pump inhibitor, omeprazole, are shown in Figure 3.

Figure 3: Impact of Other Drugs on the Pharmacokinetics of Baricitinib<sup>b</sup>

<sup>a</sup> Values are based on simulated studies.

<sup>b</sup> Reference group is administration of baricitinib alone.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of baricitinib was evaluated in Sprague-Dawley rats and Tg.rasH2 mice. No evidence of tumorigenicity was observed in male or female rats that received baricitinib for 91 to 94 weeks at oral doses up to 8 or 25 mg/kg/day, respectively (approximately 12 and 55 times the MRHD on an AUC basis). No evidence of tumorigenicity was observed in Tg.rasH2 mice that received baricitinib for 26 weeks at oral doses up to 300 and 150 mg/kg/day in male and female mice, respectively.

Baricitinib tested negative in the following genotoxicity assays: the *in vitro* bacterial mutagenicity assay (Ames assay), *in vitro* chromosome aberration assay in human peripheral blood lymphocytes, and *in vivo* rat bone marrow micronucleus assay.

Fertility (achievement of pregnancy) was reduced in male and female rats that received baricitinib at oral doses of 50 and 100 mg/kg/day respectively (approximately 113 and 169 times the MRHD in males and females, respectively, on an AUC basis) based upon findings that 7 of 19 (36.8%) drug-treated females with evidence of mating were not gravid compared to 1 of 19 (5.3%) control females. It could not be determined from the study design if these findings were attributable to toxicities in one sex or both. Fertility was unaffected in male and female rats at oral doses of 15 mg/kg and 25 mg/kg, respectively (approximately 25 and 48 times the MRHD on an AUC basis). However, maintenance of pregnancy was adversely affected at these doses based upon findings of increased post-implantation losses (early resorptions) and decreased numbers of mean viable embryos per litter. The number of viable embryos was unaffected in female rats that received baricitinib at an oral dose of 5 mg/kg/day and were mated to males that received the same dose (approximately 8 times the MRHD on an AUC basis). Reproductive performance was unaffected in male and female rats that received baricitinib at oral doses up to 50 and 100 mg/kg/day respectively (approximately 113 and 169 times the MRHD in males and females, respectively, on an AUC basis).

## 14 CLINICAL STUDIES

The OLUMIANT clinical development program included two dose-ranging trials and four confirmatory phase 3 trials. Although other doses have been studied, the recommended dose of OLUMIANT is 2 mg once daily.

### Dose-Ranging Studies

The dose-ranging studies I (NCT01185353) and II (NCT01469013) included a 12-week randomized comparison of baricitinib 1, 2, 4, and 8 mg versus placebo in 301 and 145 patients, respectively.

The results from the dose-ranging studies are shown in Table 5. In dose-ranging Study I, the observed ACR response was similar for baricitinib 1 and 2 mg daily and for baricitinib 4 and 8 mg daily, with the highest response for baricitinib 8 mg daily. In dose-ranging Study II, there was not a clear trend of dose response, with similar response rates for 1 mg and 4 mg and 2 mg and 8 mg.

**Table 5: Proportion of Patients with ACR20 Response at Week 12 in Dose-Ranging Studies**

Dose-Ranging Study	% ACR20 Responders				
	Placebo	Baricitinib 1 mg daily	Baricitinib 2 mg daily	Baricitinib 4 mg daily	Baricitinib 8 mg daily
I (N=301)	41	57	54	75	78
II (N=145)	31	67	83	67	88

### Confirmatory Studies

The efficacy and safety of OLUMIANT 2 mg once daily was assessed in two confirmatory phase 3 trials. These trials were randomized, double-blind, multicenter studies in patients with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR)/European League Against Rheumatism 2010 criteria. Patients over 18 years of age were eligible if at least 6 tender and 6 swollen joints were present at baseline. The two studies (Studies III and IV) evaluated OLUMIANT 2 mg and baricitinib 4 mg.

Study III (NCT01721057) was a 24-week trial in 684 patients with moderately to severely active rheumatoid arthritis who had an inadequate response or intolerance to conventional DMARDs (cDMARDs). Patients received OLUMIANT 2 mg or 4 mg once daily or placebo added to existing background cDMARD treatment. From Week 16, non-responding patients could be rescued to receive baricitinib 4 mg once daily. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12.

Study IV (NCT01721044) was a 24-week trial in 527 patients with moderately to severely active rheumatoid arthritis who had an inadequate response or intolerance to 1 or more TNF inhibitor therapies with or without other biologic DMARDs (TNFi-IR). Patients received OLUMIANT 2 mg or baricitinib 4 mg once daily or placebo added to background cDMARD treatment. From Week 16, non-responding patients could be rescued to receive baricitinib 4 mg once daily. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12.

### Clinical Response

The percentages of OLUMIANT-treated patients achieving ACR20, ACR50, and ACR70 responses, and Disease Activity Score (DAS28-CRP) <2.6 in Studies III and IV are shown in Table 6.

Patients treated with OLUMIANT had higher rates of ACR response and DAS28-CRP <2.6 versus placebo-treated patients at Week 12 (Studies III and IV) (Table 6).

In Study IV, higher ACR20 response rates (Figure 4) were observed as early as 1 week with OLUMIANT 2 mg versus placebo.

In Study IV, the proportions of patients achieving DAS28-CRP <2.6 who had at least 3 active joints at the end of Week 24 were 18.2% and 10.5%, in the placebo and OLUMIANT 2 mg arms, respectively.

**Table 6: Clinical Response<sup>a</sup>**

	Percent of Patients			
	cDMARD-IR		TNFi-IR	
	Study III		Study IV	
	Placebo + cDMARDs	OLUMIANT 2 mg/day + cDMARDs Δ (95% CI) <sup>b</sup>	Placebo + cDMARDs	OLUMIANT 2 mg/day + cDMARDs Δ (95% CI) <sup>b</sup>
<b>N</b>	<b>228</b>	<b>229</b>	<b>176</b>	<b>174</b>
<b>ACR 20</b>				
Week 12 %	39	66 27 (18, 35)	27	49 22 (12, 32)
Week 24 %	42	61 19 (10, 28)	27	45 18 (8, 27)
<b>ACR 50</b>				

Week 12 %	13	34 21 (13, 28)	8	20 12 (5, 19)
Week 24 %	21	41 20 (12, 28)	13	23 10 (2, 18)
<b>ACR 70</b>				
Week 12 %	3	18 15 (9, 20)	2	13 11 (5, 16)
Week 24 %	8	25 17 (11, 24)	3	13 10 (4, 16)
<b>DAS28-CRP&lt;2.6</b>				
Week 12 %	9	26 (10, 24)	4	11 (2, 12)
Week 24 %	11	31 (13, 27)	6	11 (-1, 11)

<sup>a</sup> Patients who were rescued or discontinued treatment were considered as non-responders in the analyses.

<sup>b</sup> 95% confidence interval for the difference ( $\Delta$ ) in response rate between OLUMIANT treatment and placebo (Study III, Study IV).

The effects of OLUMIANT treatment on the components of the ACR response criteria for Studies III and IV are shown in Table 7.

**Table 7: Components of ACR Response at Week 12 in Studies III and IV<sup>a</sup>**

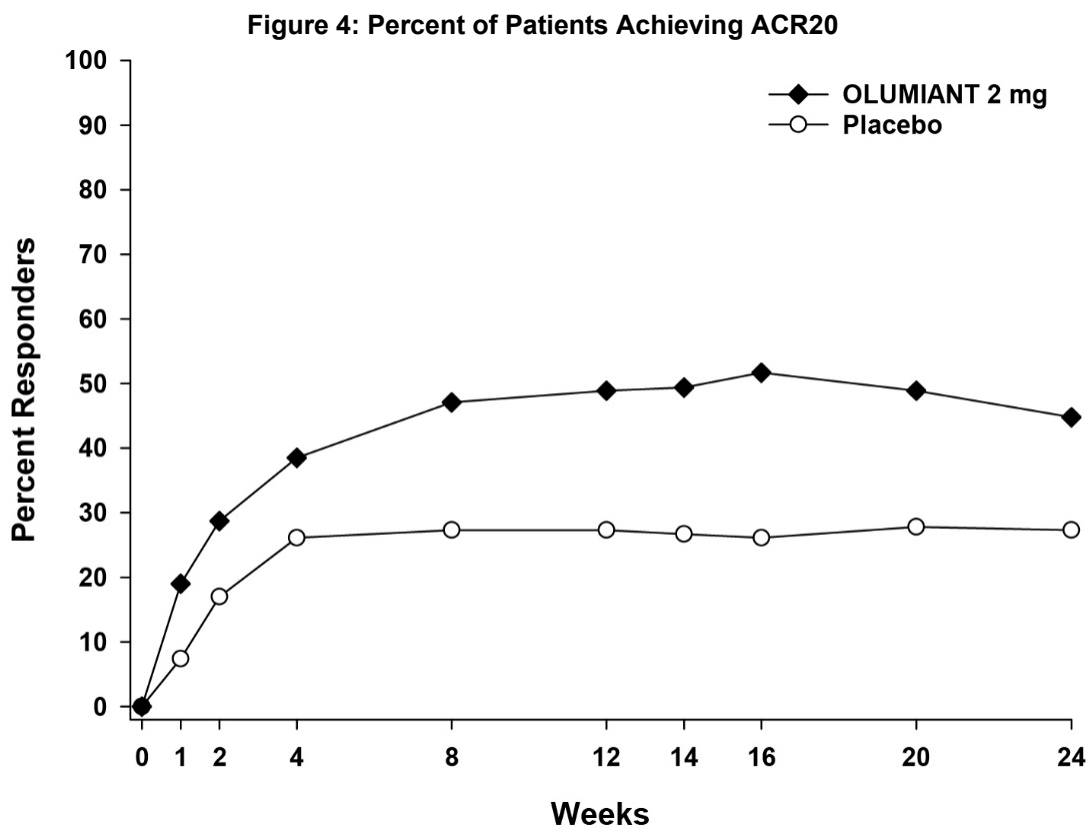
	cDMARD-IR		TNFi-IR	
	Study III		Study IV	
	Placebo + cDMARDs	OLUMIANT 2 mg/day + cDMARDs	Placebo + cDMARDs	OLUMIANT 2 mg/day + cDMARDs
<b>N</b>	<b>228</b>	<b>229</b>	<b>176</b>	<b>174</b>
<b>Number of Tender Joints (0-68)</b>				
Baseline	24 (15)	24 (14)	28 (16)	31 (16)
Week 12	15 (14)	11 (13)	20 (16)	19 (18)
<b>Number of Swollen Joints (0-66)</b>				
Baseline	13 (7)	14 (9)	17 (11)	19 (12)
Week 12	8 (8)	5 (6)	12 (10)	10 (12)
<b>Pain<sup>b</sup></b>				
Baseline	57 (23)	60 (21)	65 (19)	62 (22)
Week 12	43 (24)	34 (25)	55 (25)	46 (28)
<b>Patient Global Assessment<sup>b</sup></b>				
Baseline	60 (21)	62 (20)	66 (19)	67 (19)
Week 12	44 (23)	36 (25)	56 (25)	46 (26)
<b>Physician Global Assessment<sup>b</sup></b>				
Baseline	62 (17)	64 (17)	67 (19)	67 (17)
Week 12	41 (24)	33 (22)	50 (26)	36 (24)
<b>Disability Index (HAQ-DI)<sup>c</sup></b>				
Baseline	1.50 (0.60)	1.51 (0.62)	1.78 (0.57)	1.71 (0.55)
Week 12	1.17 (0.62)	0.96 (0.69)	1.59 (0.68)	1.31 (0.72)
<b>hsCRP (mg/L)</b>				
Baseline	17.7 (20.4)	18.2 (21.5)	20.6 (25.3)	19.9 (22.5)
Week 12	17.2 (19.3)	8.6 (14.6)	19.9 (23.0)	13.5 (20.1)



<sup>a</sup> Data shown are mean (standard deviation).

<sup>b</sup> Visual analog scale: 0=best, 100=worst.

<sup>c</sup> Health Assessment Questionnaire–Disability Index: 0=best, 3=worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.



### Physical Function Response

Improvement in physical function was measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI). Patients receiving OLUMIANT 2 mg demonstrated greater improvement from baseline in physical functioning compared to placebo at Week 24. The mean difference (95% CI) from placebo in HAQ-DI change from baseline at Week 24 was -0.24 (-0.35, -0.14) in Study III and -0.23 (-0.35, -0.12) in Study IV.

### Other Health Related Outcomes

General health status was assessed by the Short Form health survey (SF-36). In Studies III and IV, compared to placebo, patients treated with OLUMIANT 2 mg demonstrated greater improvement from baseline in the physical component summary (PCS) score and the physical function, role physical, bodily pain, vitality, and general health domains at Week 12, with no consistent improvements in the mental component summary (MCS) scores or the role emotional, mental health, and social functioning domains.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

### **16.1 How Supplied**

OLUMIANT for oral administration is available as debossed, film-coated, immediate-release tablets. Each tablet contains a recessed area on each face of the tablet surface.

<b>OLUMIANT Tablets</b>	2 mg
<b>Color</b>	Light Pink
<b>Shape</b>	Oblong
<b>Identification</b>	Lilly 2
<b>NDC Code:</b>	

Bottle of 30

0002-4182-30

**16.2 Storage and Handling**

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Keep out of reach of children.

**17 PATIENT COUNSELING INFORMATION**

See FDA-approved patient labeling (Medication Guide).

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

**Patient Counseling**

Advise patients of the potential benefits and risks of OLUMIANT.

**Infections**

Inform patients that they may be more likely to develop infections when taking OLUMIANT. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of an infection [see Warnings and Precautions (5.1)].

Advise patients that the risk of herpes zoster is increased in patients treated with OLUMIANT and some cases can be serious [see Warnings and Precautions (5.1)].

**Malignancies and Lymphoproliferative Disorders**

Inform patients that OLUMIANT may increase their risk of certain cancers, and that lymphoma and other cancers have been observed in patients taking OLUMIANT. Instruct patients to inform their healthcare provider if they have ever had any type of cancer [see Warnings and Precautions (5.2)].

**Thrombosis**

Advise patients that events of DVT and PE have been reported in clinical studies with OLUMIANT. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE [see Warnings and Precautions (5.3)].

**Laboratory Abnormalities**

Inform patients that OLUMIANT may affect certain lab tests, and that blood tests are required before and during OLUMIANT treatment [see Warnings and Precautions (5.5)].

**Lactation**

Advise a woman not to breastfeed during treatment with OLUMIANT [see Use in Specific Populations (8.2)].

Literature issued Month dd, yyyy

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**www.olumiant.com**

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**MEDICATION GUIDE**  
**OLUMIANT® (O-loo-me-ant)**  
**(baricitinib)**  
**tablets, for oral use**

**What is the most important information I should know about OLUMIANT?**

**OLUMIANT may cause serious side effects, including:**

**1. Serious infections.**

OLUMIANT is a medicine that affects your immune system. OLUMIANT can lower the ability of your immune system to fight infections. Some people have had serious infections while taking OLUMIANT, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections.

- Your healthcare provider should test you for TB before starting treatment with OLUMIANT.
- Your healthcare provider should watch you closely for signs and symptoms of TB during treatment with OLUMIANT.

You should not start taking OLUMIANT if you have any kind of infection unless your healthcare provider tells you it is okay. You may be at a higher risk of developing shingles.

Before starting OLUMIANT, tell your healthcare provider if you:

- are being treated for an infection.
- have an infection that does not go away or that keeps coming back.
- have diabetes, chronic lung disease, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB or have been in close contact with someone with TB.
- have had hepatitis B or C.
- live or have lived, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections. These infections may happen or become more severe if you use OLUMIANT. Ask your healthcare provider if you do not know if you have lived in an area where these infections are common.
- think you have an infection or have symptoms of an infection such as:
  - fever, sweating, or chills
  - shortness of breath
  - warm, red, or painful skin or sores on your body
  - feeling tired
  - muscle aches
  - blood in your phlegm
  - diarrhea or stomach pain
  - cough
  - weight loss
  - burning when you urinate or urinating more often than normal

After starting OLUMIANT, call your healthcare provider right away if you have any symptoms of an infection. OLUMIANT can make you more likely to get infections or make worse any infection that you have.

**2. Cancer and immune system problems.**

OLUMIANT may increase your risk of certain cancers by changing the way your immune system works.

- Lymphoma and other cancers including skin cancers can happen in people taking OLUMIANT. Tell your healthcare provider if you have ever had any type of cancer.

**3. Blood Clots.**

Blood clots in the veins of your legs (deep vein thrombosis, DVT) or lungs (pulmonary embolism, PE) can happen in some people taking OLUMIANT. This may be life-threatening and cause death.

- Tell your healthcare provider if you have had blood clots in the veins of your legs or lungs in the past.
- Tell your healthcare provider right away if you have any signs and symptoms of blood clots during treatment with OLUMIANT, including: swelling, pain or tenderness in the leg, sudden unexplained chest pain, or shortness of breath.

**4. Tears (perforation) in the stomach or intestines.**

- Tell your healthcare provider if you have had diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people taking OLUMIANT can get tears in their stomach or intestines. This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.
- Tell your healthcare provider right away if you have fever and stomach-area pain that does not go away, and a change in your bowel habits.

**5. Changes in certain laboratory test results.**

Your healthcare provider should do blood tests before you start taking OLUMIANT and while you take OLUMIANT to check for the following:

- **low lymphocyte counts.** Lymphocytes are white blood cells that help the body fight off infections.
- **low neutrophil counts.** Neutrophils are white blood cells that help the body fight off infections.
- **low red blood cell counts.** This may mean that you have anemia, which may make you feel weak and tired.

Your healthcare provider should routinely check certain liver tests.

You should not receive OLUMIANT if your lymphocyte count, neutrophil count, or red blood cell count is too low or your liver tests are too high.

Your healthcare provider may stop your OLUMIANT treatment for a period of time if needed because of changes in these blood test results.

You may also have changes in other laboratory tests, such as your blood cholesterol levels. Your healthcare provider should do blood tests to check your cholesterol levels approximately 12 weeks after you start taking OLUMIANT, and as needed after that. Normal cholesterol levels are important to good heart health.

See "**What are the possible side effects of OLUMIANT?**" for more information about side effects.

#### **What is OLUMIANT?**

- OLUMIANT is a prescription medicine used to treat adult patients with moderately to severely active rheumatoid arthritis after treatment with at least one other medicine called a Tumor Necrosis Factor (TNF) antagonist has been used, and did not work well enough or could not be tolerated.
- It is not known if OLUMIANT is safe and effective in children.

#### **Before taking OLUMIANT, tell your healthcare provider about all your medical conditions, including if you:**

- See "**What is the most important information I should know about OLUMIANT?**"
- have an infection.
- have kidney problems.
- have liver problems.
- have low red or white blood cell counts.
- have recently received or are scheduled to receive a vaccine. People who take OLUMIANT should not receive live vaccines.
- have any stomach area (abdominal) pain or been diagnosed with diverticulitis or ulcers in your stomach or intestines.
- are pregnant or plan to become pregnant. It is not known if OLUMIANT will harm an unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if OLUMIANT passes into your breast milk. You and your healthcare provider should decide if you will take OLUMIANT or breastfeed. You should not do both.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. OLUMIANT and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:

- a medicine called probenecid.
- any other medicines to treat your rheumatoid arthritis. For example, you should not take tocilizumab (Actemra<sup>®</sup>), etanercept (Enbrel<sup>®</sup>), adalimumab (Humira<sup>®</sup>), infliximab (Remicade<sup>®</sup>), rituximab (Rituxan<sup>®</sup>), abatacept (Orencia<sup>®</sup>), anakinra (Kineret<sup>®</sup>), certolizumab pegol (Cimzia<sup>®</sup>), golimumab (Simponi<sup>®</sup>), tofacitinib (Xeljanz<sup>®</sup>, Xeljanz<sup>®</sup> XR), sarilumab (Kevzara<sup>®</sup>), azathioprine or cyclosporine while you are taking OLUMIANT. Taking OLUMIANT with these medicines may increase your risk of infection.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

#### **How should I take OLUMIANT?**

- Take OLUMIANT exactly as your healthcare provider tells you to take it.
- Take OLUMIANT 1 time a day with or without food.

#### **What are the possible side effects of OLUMIANT?**

**OLUMIANT can cause serious side effects including:**

- See "**What is the most important information I should know about OLUMIANT?**"

Common side effects of OLUMIANT include (these are not all of the possible side effects of OLUMIANT):

- upper respiratory tract infections (common cold, sinus infections)
- cold sores
- nausea
- shingles

**Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

#### **How should I store OLUMIANT?**

Store OLUMIANT at room temperature between 68°F to 77°F (20°C to 25°C).

**Keep OLUMIANT and all medicines out of the reach of children.**

#### **General Information about the safe and effective use of OLUMIANT.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use OLUMIANT for a condition for which it was not prescribed. Do not give OLUMIANT to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about OLUMIANT that is written for health professionals.

#### **What are the ingredients in OLUMIANT?**

**Active ingredient:** baricitinib

**Inactive ingredients:** croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, ferric oxide, lecithin (soya), polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide.

OLUMIANT is a registered trademark of Eli Lilly and Company.

**Marketed by: Lilly USA, LLC Indianapolis, IN 46285, USA**

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For more information, call 1-800-545-5979 or go to the following website: [www.olumiant.com](http://www.olumiant.com).


This Medication Guide has been approved by the U.S. Food and Drug Administration

Issued: 05/2018

BAR-A3.0-0000-MG-YYYYMMDD

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0002-4182-30  
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NL0521DAM00    GTIN: 00300024182301  
Exp. Date / Control No. / Serial No.

**Rx only**


**ALWAYS DISPENSE WITH  
MEDICATION GUIDE**

NDC 0002-4182-30

**olumiant.**  
(baricitinib) tablets

**2 mg**

**30 tablets**



**Do not use if inner seal is missing or broken.**  
Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].  
Keep out of reach of children.

Usual dosage: See Prescribing Information.

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/s/  
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MARY T THANH HAI  
05/31/2018