

**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, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), AND THROMBOSIS**

See full prescribing information for complete boxed warning.

- Increased risk of serious bacterial, fungal, viral and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). Interrupt treatment with OLUMIANT if serious infection occurs until the infection is controlled. Test for latent TB before and during therapy; treat latent TB prior to use. Monitor all patients for active TB during treatment, even patients with initial negative, latent TB test. (5.1)
- Higher rate of all-cause mortality, including sudden cardiovascular death with another Janus kinase inhibitor (JAK) vs. TNF blockers in rheumatoid arthritis (RA) patients. (5.2)
- Malignancies have occurred in patients treated with OLUMIANT. Higher rate of lymphomas and lung cancers with another JAK inhibitor vs. TNF blockers in RA patients. (5.3)
- Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) with another JAK inhibitor vs. TNF blockers in RA patients. (5.4)
- Thrombosis has occurred in patients treated with OLUMIANT. Increased incidence of pulmonary embolism, venous and arterial thrombosis with another JAK inhibitor vs. TNF blockers. (5.5)

-----RECENT MAJOR CHANGES-----

Boxed Warning	12/2021
Warnings and Precautions, Mortality (5.2)	12/2021
Warnings and Precautions, Malignancy and Lymphoproliferative Disorders (5.3)	12/2021
Warnings and Precautions, Major Adverse Cardiovascular Events (5.4)	12/2021
Warnings and Precautions, Thrombosis (5.5)	12/2021

-----INDICATIONS AND USAGE-----

OLUMIANT® is a Janus kinase (JAK) inhibitor 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 blockers. (1.1)

Limitation of Use: Not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine. (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)
- Cytopenias: Avoid initiation or interrupt OLUMIANT in patients with anemia (hemoglobin <8 g/dL), lymphopenia (ALC <500 cells/mm<sup>3</sup>) and neutropenia (ANC <1000 cells/mm<sup>3</sup>). (2.2, 2.3, 5.7)
- Moderate Renal Impairment: Reduce dose to 1 mg once daily. (2.4)

-----DOSAGE FORMS AND STRENGTHS-----

Tablets: 2 mg, 1 mg (3)

-----CONTRAINDICATIONS-----

None.

-----WARNINGS AND PRECAUTIONS-----

- Gastrointestinal Perforations: Use with caution in patients at risk. (5.6)
- Laboratory Assessment: Monitor for changes in lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids. (5.7)
- Vaccinations: Avoid use with live vaccines. (5.8)
- Hypersensitivity: Serious reactions have been reported. (5.9)

-----ADVERSE REACTIONS-----

Adverse reactions (≥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-----

The recommended dose of OLUMIANT in patients taking strong Organic Anion Transporter 3 (OAT3) inhibitors (e.g., probenecid) is 1 mg once daily. (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 severe renal impairment. (2.4, 8.7)

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

Revised: 12/2021

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## FULL PRESCRIBING INFORMATION

### WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, 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. If positive, start treatment for latent infection 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)*].

#### MORTALITY

In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing another Janus kinase (JAK) inhibitor to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor [see *Warnings and Precautions (5.2)*].

#### MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with OLUMIANT. In RA patients treated with another JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk [see *Warnings and Precautions (5.3)*].

#### MAJOR ADVERSE CARDIOVASCULAR EVENTS

In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue OLUMIANT in patients that have experienced a myocardial infarction or stroke [see *Warnings and Precautions (5.4)*].

#### 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. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid OLUMIANT in patients at risk. Patients with symptoms of thrombosis should discontinue OLUMIANT and be promptly evaluated. [see *Warnings and Precautions (5.5)*].

## 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) blockers.

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

## 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* (5.7)].
- 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, start treatment 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

- The recommended dose of OLUMIANT in patients with moderate renal impairment (estimated glomerular filtration rate (GFR) between 30 and 60 mL/min/1.73 m<sup>2</sup>) is 1 mg once daily. OLUMIANT is not recommended for use in patients with severe renal impairment (estimated GFR of less than 30 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

The recommended dose of OLUMIANT in patients taking strong Organic Anion Transporter 3 (OAT3) inhibitors, such as probenecid, is 1 mg once daily [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:

- 1 mg tablet contains a recessed area on each face of the tablet surface, is very light pink, round, debossed with "Lilly" on one side and "1" on the other.
- 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 Mortality

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed in patients treated with the JAK inhibitor compared with TNF blockers. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OLUMIANT.

## 5.3 Malignancy and Lymphoproliferative Disorders

Malignancies were observed in clinical studies of OLUMIANT [see *Adverse Reactions (6.1)*].

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lymphomas was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lung cancers was observed in current or past smokers treated with the JAK inhibitor compared to those treated with TNF blockers. In this study, current or past smokers had an additional increased risk of overall malignancies.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OLUMIANT, particularly in patients with a known malignancy (other than successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

### 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.

## 5.4 Major Adverse Cardiovascular Events

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke was observed with the JAK inhibitor compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OLUMIANT, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue OLUMIANT in patients that have experienced a myocardial infarction or stroke.

### 5.5 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. In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, higher rates of overall thrombosis, DVT, and PE were observed compared to those treated with TNF blockers.

If clinical features of DVT/PE or arterial thrombosis occur, patients should discontinue OLUMIANT and be evaluated promptly and treated appropriately. Avoid OLUMIANT in patients that may be at increased risk of thrombosis.

### 5.6 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.

### 5.7 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. Adjust dosing 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. Adjust dosing based on ALC [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. Adjust dosing based on hemoglobin levels [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 of ALT  $\geq$ 5 times the upper limit of normal (ULN) and increases of AST  $\geq$ 10 times the ULN were observed 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.

### 5.8 Vaccinations

Avoid use of live vaccines with OLUMIANT.

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

### 5.9 Hypersensitivity

Reactions such as angioedema, urticaria, and rash that may reflect drug hypersensitivity have been observed in patients receiving OLUMIANT, including serious reactions. If a serious hypersensitivity reaction occurs, promptly discontinue OLUMIANT while evaluating the potential causes of the reaction [see *Adverse Reactions (6.2)*].

## 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 patients-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 (5.3)*].

**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, 5.7)*].

**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  $\geq 3$  times the ULN were observed in patients treated with OLUMIANT [see *Warnings and Precautions* (5.7)].

- During the 16-week treatment period, ALT elevations  $\geq 3$  times the 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  $\geq 3$  times the 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  $\geq 3$  times the 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* (5.7)].

**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**

Events	Weeks 0-16		
	Placebo n=1070 (%)	OLUMIANT 2 mg n=479 (%)	Baricitinib 4 mg n=997 (%)
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.

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of OLUMIANT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Immune System Disorders:** Drug hypersensitivity (events such as rash, urticaria, and angioedema have been observed) [see *Warnings and Precautions* (5.9)].

## 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  $AUC_{0-1}$  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. The recommended dose of OLUMIANT in patients with moderate renal impairment (estimated glomerular filtration rate (GFR) between 30 and 60 mL/min/1.73 m<sup>2</sup>) is 1 mg once daily. OLUMIANT is not recommended for use in patients with severe renal impairment (estimated GFR of less than 30 mL/min/1.73 m<sup>2</sup>) [see *Dosage and Administration* (2.4) and *Clinical Pharmacology* (12.3)].

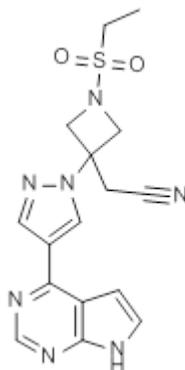
### 10 OVERDOSAGE

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 1 mg tablet is very light pink, round, debossed with "Lilly" on one side and "1" on the other. The 2 mg tablet is light pink, oblong, debossed with "Lilly" on one side and "2" on the other.

Each tablet contains 1 or 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)*].

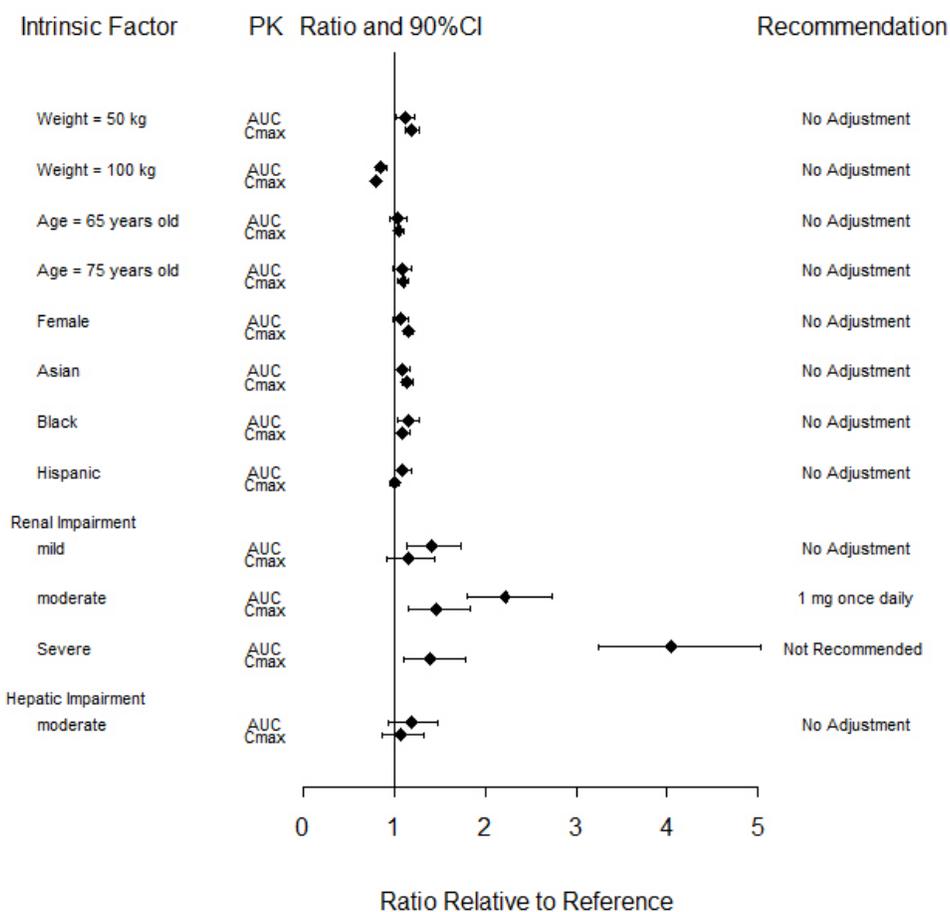
### *Renal Impairment*

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

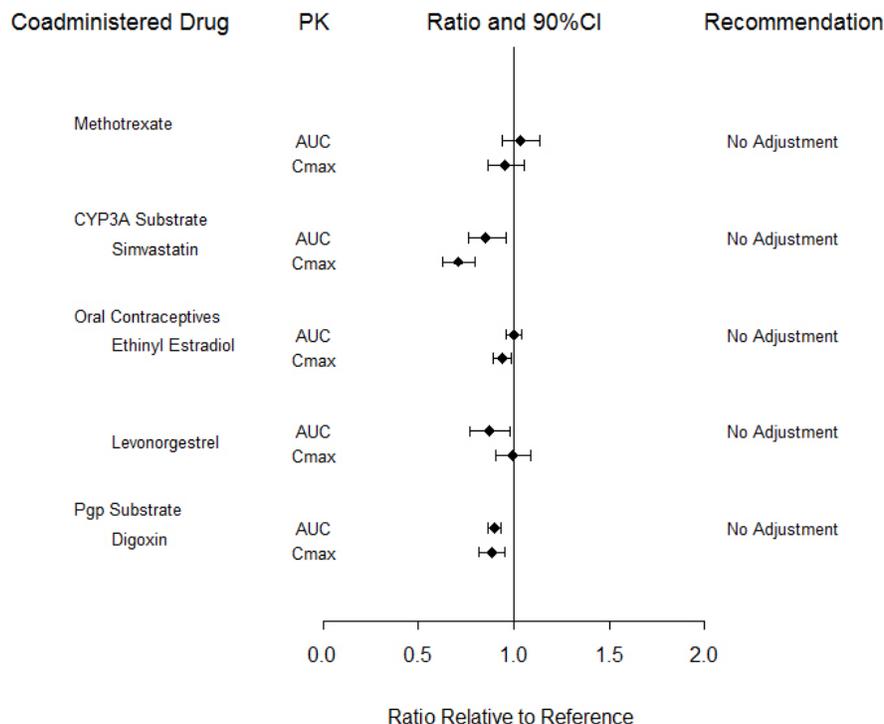
#### *Potential for Baricitinib to Influence the PK of Other Drugs*

*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>**



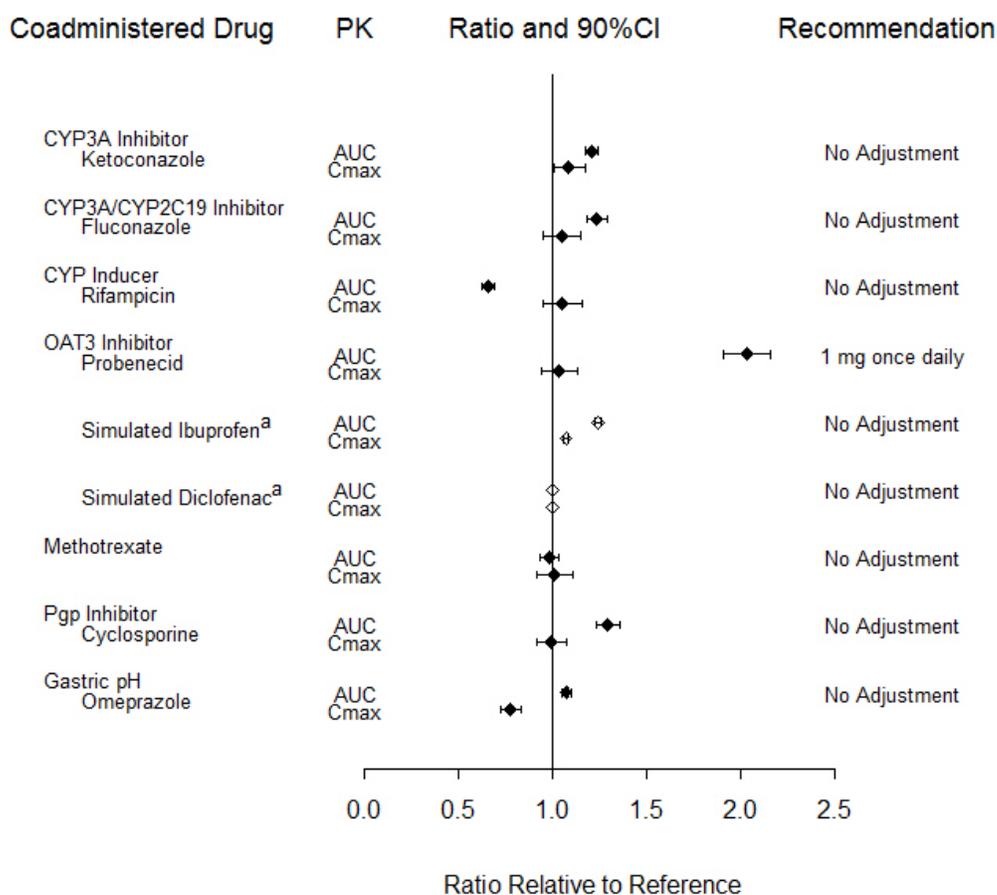
<sup>a</sup> Reference group is administration of concomitant drug alone.

#### *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>**

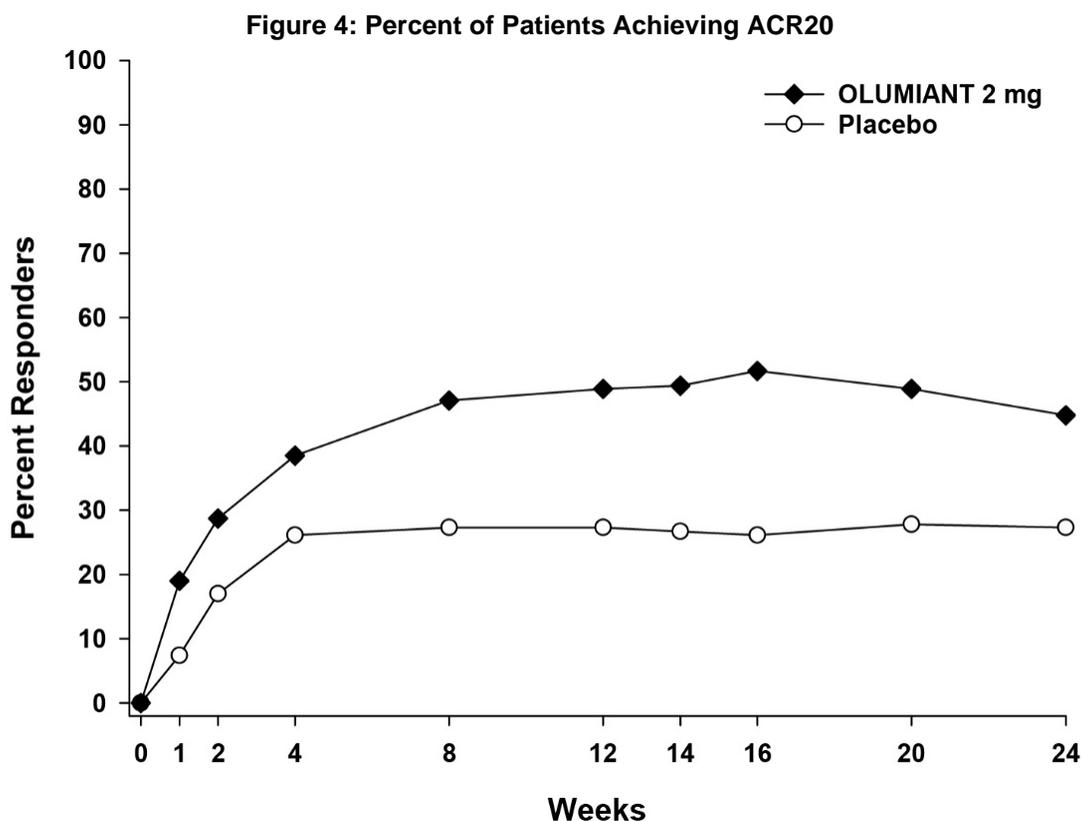
	cDMARD-IR		TNFi-IR	
	Study III		Study IV	
	Placebo + cDMARDs	OLUMIANT 2 mg/day + cDMARDs	Placebo + cDMARDs	OLUMIANT 2 mg/day + cDMARDs
<b>N</b>	<b>228</b>	<b>229</b>	<b>176</b>	<b>174</b>
<b>Number of Tender Joints (0-68)</b>				
Baseline	24 (15)	24 (14)	28 (16)	31 (16)
Week 12	15 (14)	11 (13)	20 (16)	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)

hsCRP (mg/L)				
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.

OLUMIANT Tablets	1 mg	2 mg
Color	Very Light Pink	Light Pink
Shape	Round	Oblong

<b>Identification</b>	Lilly 1	Lilly 2
<b>NDC Codes:</b>		
<b>Bottle of 30</b>	0002-4732-30	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

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 developing lymphomas and other malignancies, including of the skin. Instruct patients to inform their healthcare provider if they have ever had any type of cancer [see *Warnings and Precautions (5.3)*].

### Major Adverse Cardiovascular Events

Inform patients that OLUMIANT may increase their risk of major adverse cardiovascular events (MACE) including myocardial infarction, stroke, and cardiovascular death. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events [see *Warnings and Precautions (5.4)*].

### 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 (5.5)*].

### 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 (5.7)*].

### Lactation

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

Literature revised: 00/0000

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