PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrOLUMIANT™

baricitinib

2 mg baricitinib, tablets, oral

ATC Code: L04AA37
Selective Immunosuppressant

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PrOLUMIANT™

baricitinib tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Tablets / 2 mg	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

OLUMIANT (baricitinib), in combination with methotrexate (MTX), is indicated for reducing the signs and symptoms of moderate to severe rheumatoid arthritis (RA) in adult patients who have responded inadequately to one or more disease-modifying anti-rheumatic drugs (DMARDs).

OLUMIANT may be used as monotherapy in cases of intolerance to MTX.

Limitations of Use: Use of OLUMIANT in combination with other JAK inhibitors, biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended (see WARNINGS AND PRECAUTIONS, Immune).

Geriatrics (≥65 years of age): Caution should be used when treating the elderly with OLUMIANT as the greater sensitivity of some older individuals cannot be ruled out (see WARNINGS AND PRECAUTIONS, Special Populations, DOSAGE AND ADMINISTRATION, Dosing in Special Populations, and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Pediatrics (<18 years of age): The safety and effectiveness of OLUMIANT in pediatric patients have not been established. Therefore, OLUMIANT should not be used in this patient population (see WARNINGS AND PRECAUTIONS, Special Populations, DOSAGE AND ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

CONTRAINDICATIONS

OLUMIANT is contraindicated in patients with known hypersensitivity to baricitinib or any of its components. For a complete listing, see DOSAGE FORMS, COMPOSITION and PACKAGING section.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

SERIOUS INFECTIONS
Patients treated with OLUMIANT (baricitinib) are at risk for developing serious infections that may lead to hospitalization or death. 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 initiated prior to OLUMIANT use.
- Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized disease.
- Bacterial, viral, and other infections due to opportunistic pathogens.

Treatment with OLUMIANT should not be initiated in patients with active infections including chronic or localized 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, Infections, and ADVERSE REACTIONS).

MALIGNANCIES
Lymphoma and other malignancies have been observed in patients treated with OLUMIANT (see WARNINGS AND PRECAUTIONS, Malignancies).

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, Cardiovascular).

Cardiovascular

Thrombosis: Thrombosis, including deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving OLUMIANT in clinical trials and in the post-market setting. Arterial thrombosis events in the extremities have also been reported in clinical studies with OLUMIANT. Many of these adverse events were serious and some resulted in death (see ADVERSE REACTIONS).

Recurrent events of venous thrombosis have been reported in some patients recommencing treatment with OLUMIANT. OLUMIANT should be used with caution in patients with risk factors for DVT/PE. Consideration should be given to temporary interruption of OLUMIANT in patients undergoing major surgery or prolonged immobilization. Patients with multiple risk factors for VTE and patients with known thrombophilia should be closely monitored and consideration should be given to appropriate VTE prophylaxis if the benefits of OLUMIANT treatment are considered to outweigh the risks for the individual patient.

If clinical features of DVT/PE or arterial thrombosis occur, interrupt OLUMIANT, evaluate promptly, and institute appropriate treatment.

Gastrointestinal

Gastrointestinal Perforations: Events of gastrointestinal perforation have been reported in clinical trials with OLUMIANT in rheumatoid arthritis patients, 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., use of concomitant NSAIDs and/or corticosteroids, patients with a history of diverticulitis). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation (see ADVERSE REACTIONS).

Hepatic

Treatment with OLUMIANT was associated with an increased incidence of liver enzyme elevation compared to placebo. Increases to ≥5X and 10X upper limit of normal (ULN) were observed for both ALT and AST in patients treated with OLUMIANT in clinical trials. Unconfirmed drug induced liver injury (DILI) was observed in four patients receiving baricitinib 4 mg in clinical trials. Baricitinib was discontinued in 2 cases, temporarily interrupted and resumed in 1 case, and continued without interruption in 1 case.

Evaluate liver enzymes before initiating OLUMIANT and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of DILI. If increases in ALT or AST are observed and DILI is suspected, interrupt OLUMIANT until the diagnosis is excluded (see WARNINGS AND PRECAUTIONS, Laboratory Parameters, and Monitoring and Laboratory Tests, and ADVERSE REACTIONS).

The use of baricitinib has not been studied in patients with severe hepatic impairment and is therefore not recommended.

Immune

OLUMIANT can increase the risk of infections and immunosuppression when coadministered with potent immunosuppressants such as cyclosporine, azathioprine and tacrolimus. Combined use of OLUMIANT with potent immunosuppressive drugs has not been studied in rheumatoid arthritis patients and is not recommended (see DRUG INTERACTIONS).

Immunizations

The use of OLUMIANT with live vaccines is not recommended. Update immunizations in agreement with current immunization guidelines prior to initiating OLUMIANT therapy. The

interval between live vaccinations and initiation of OLUMIANT therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

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 immunosuppressive agents, including biologic DMARDs and OLUMIANT. The most common serious infections reported with OLUMIANT included pneumonia, herpes zoster, and urinary tract infections (see ADVERSE REACTIONS). 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 infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating OLUMIANT in patients:

- With chronic or recurrent infections
- Who have been exposed to tuberculosis
- With a history of a serious or an opportunistic infection
- Who have resided or travelled 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.

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when using OLUMIANT in these populations (see WARNINGS AND PRECAUTIONS, Special Populations). Caution is also recommended in patients with a history of chronic lung disease, as they may be more prone to infections. Events of interstitial lung disease have been reported in patients treated with OLUMIANT in clinical trials (see WARNINGS AND PRECAUTIONS, Respiratory).

Risk of infection may be higher with increasing degrees of lymphopenia and consideration should be given to lymphocyte counts when assessing individual patient risk of infection. For discontinuation and monitoring criteria for lymphopenia (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Tuberculosis (TB) – Evaluate and test patients for latent or active infection prior to administration of OLUMIANT. OLUMIANT should not be given to patients with active TB.

Consider anti-TB therapy prior to initiation of OLUMIANT in patients with previously untreated latent TB. 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 observed in clinical studies with OLUMIANT. If a patient develops herpes zoster, OLUMIANT treatment should be interrupted 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.

Laboratory Parameters

Creatine phosphokinase (CPK): OLUMIANT treatment was associated with dose-dependent 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 U/L and 52 U/L, respectively (see WARNINGS AND PRECAUTIONS, Musculoskeletal, and ADVERSE REACTIONS).

Hematology:

Hemoglobin*:* Dose-dependent decreases in hemoglobin levels to <80 g/L were reported with OLUMIANT treatment in clinical trials. Avoid initiation or interrupt OLUMIANT treatment in patients with hemoglobin <80 g/L. Evaluate hemoglobin prior to initiation of OLUMIANT and thereafter according to routine patient management (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, and DOSAGE AND ADMINISTRATION).

Lymphopenia*:* Dose-dependent absolute decreases in Lymphocyte Count (ALC) <0.5 x 10^9 cells/L 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 <0.5 x 10^9 cells/L. Evaluate lymphocytes prior to initiation of OLUMIANT and thereafter according to routine patient management (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, DOSAGE AND ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY).

The risk of lymphocytosis is increased in elderly patients with rheumatoid arthritis. Rare cases of lymphoproliferative disorders have been reported.

Neutropenia*:* Treatment with OLUMIANT was associated with a dose-dependent increased incidence of neutropenia (ANC <1 x 10^9 cells/L) compared to placebo. Avoid initiation or interrupt OLUMIANT treatment in patients with an ANC <1 x 10^9 cells/L. Evaluate neutrophils prior to initiating OLUMIANT and thereafter according to routine patient management (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS).

Pancytopenia*:* Events of pancytopenia have been reported in patients with rheumatoid arthritis taking OLUMIANT in clinical trials. In all cases, pancytopenia occurred in patients who reported potential confounding factors (concurrent events or recent medication changes) that may have contributed to the observed pancytopenia (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Platelets and thrombocytosis*:* In controlled studies, dose-dependent, treatment-emergent increases in platelet counts were seen in patients treated with OLUMIANT compared to placebo. The clinical significance of this finding is not known. There was no clear association between increased platelet counts and the adverse events of a thrombotic nature that were reported in the clinical trials (see WARNINGS AND PRECAUTIONS, Cardiovascular, and ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings).

Lipids: Dose-dependent increases in lipid parameters (LDL cholesterol and triglycerides) were very common in patients treated with OLUMIANT compared to placebo in clinical trials (see ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings). Assessment of lipid parameters should be performed approximately 12 weeks following initiation of OLUMIANT and as needed thereafter. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Manage patients according to clinical guidelines (e.g., Canadian Cardiovascular Society [CCS]) for the management of hyperlipidemia. Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy for patients receiving OLUMIANT (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, and ADVERSE REACTIONS).

Liver Enzymes: Increases to ≥5 and ≥10 X upper limit of normal (ULN) were observed for both ALT and AST in patients treated with OLUMIANT in clinical trials. See WARNINGS AND PRECAUTIONS, Hepatic, and Monitoring and Laboratory Tests, and ADVERSE REACTIONS.

Renal Function: Dose-dependent increases in creatinine and urea nitrogen and decreases in eGFR and creatinine clearance were observed in clinical trials with OLUMIANT. See WARNINGS AND PRECAUTIONS, Renal, ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings, DOSAGE AND ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY.

Malignancies

The risk of malignancies including lymphoma is increased in patients with rheumatoid arthritis. Treatment with immunosuppressants may result in an increased risk of malignancies. Malignancies have been observed in patients treated with OLUMIANT (see ADVERSE REACTIONS). 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 (see ADVERSE REACTIONS, Malignancy).
NMSCs have been reported in patients treated with OLUMIANT. Periodic skin examination is recommended for patients who are at increased risk for skin cancer (see ADVERSE REACTIONS, Malignancy).

Musculoskeletal
Treatment with OLUMIANT was associated with dose-dependent increases in creatine phosphokinase (CPK). CPK levels should be checked in patients with symptoms of muscle weakness and/or muscle pain to evaluate for evidence of rhabdomyolysis (see ADVERSE REACTIONS).

Renal
OLUMIANT is not recommended for use in patients with an estimated GFR of less than 60 mL/min/1.73 m^2 (moderate and severe renal impairment including ESRD patients). Renal function was found to significantly affect baricitinib exposure. 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. Dose-dependent increases in creatinine and urea nitrogen, and decreases in eGFR and creatinine clearance were observed in clinical trials with OLUMIANT (see DOSAGE AND ADMINISTRATION, Dosing in Special Populations, and ACTION AND CLINICAL PHARMACOLOGY).

Respiratory
Interstitial Lung Disease (ILD): Events of ILD have been reported in clinical trials and post-market with OLUMIANT in rheumatoid arthritis patients. Although the role of JAK inhibition in these events is not known, the events of ILD were considered possibly related to OLUMIANT treatment in some cases. Most patients who developed ILD were taking concomitant methotrexate, which has been associated with ILD. OLUMIANT should be used with caution in patients with risk factors for, or a history of, ILD.

Special Populations

Pregnant Women: OLUMIANT should not be used during pregnancy. There are no adequate and well-controlled studies to assess the use of OLUMIANT in pregnant women. OLUMIANT has been shown to be teratogenic in rats and rabbits and have effects in rats on female fertility, parturition, and peri/postnatal development (see TOXICOLOGY).

Women of reproductive potential should be advised to take appropriate precautions to avoid becoming pregnant during treatment with OLUMIANT and for at least 1 week after the final treatment. If the patient becomes pregnant while taking OLUMIANT, or if OLUMIANT is used during pregnancy, inform the patient of the potential for hazard to a fetus.

Nursing Women: Breastfeeding is not recommended during OLUMIANT treatment. Lactation studies have not been conducted to assess the presence of baricitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Baricitinib was secreted in the milk of lactating rats and absorbed by suckling pups (see TOXICOLOGY).

Pediatrics (<18 years of age): The safety and effectiveness of OLUMIANT in pediatric patients have not been established. Therefore, OLUMIANT should not be used in this patient population (see DOSAGE AND ADMINISTRATION, Dosing in Special Populations and ACTION AND CLINICAL PHARMACOLOGY).

Geriatrics (≥65 years of age): Caution should be used when treating the elderly with OLUMIANT as the greater sensitivity of some older individuals cannot be ruled out. The incidence of fatal serious adverse events (SAEs), hospitalization due to SAEs, life-threatening SAEs, and AEs leading to study medication discontinuation was highest in the 75 to 84 year old subgroup, compared to the younger subgroups. 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, it may be useful to closely monitor renal function in this population (see DOSAGE AND ADMINISTRATION, Dosing in Special Populations and ACTION AND CLINICAL PHARMACOLOGY).

Monitoring and Laboratory Tests
Lipid tests: Assessment of lipid parameters should be performed prior to starting OLUMIANT, approximately 12 weeks after initiation of treatment and periodically thereafter.

Hepatic tests: Liver enzyme tests are recommended. If drug-induced liver injury is suspected, the administration of OLUMIANT should be interrupted until this diagnosis has been excluded.

Renal tests: Assessment of renal function is recommended prior to initiation of OLUMIANT, approximately 4-8 weeks after initiation with OLUMIANT and periodically thereafter.

Hematology: Lymphocyte counts, neutrophil counts, and hemoglobin should be tested at baseline, approximately 4-8 weeks after initiation with OLUMIANT and periodically thereafter.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

A total of 3492 rheumatoid arthritis patients were treated with OLUMIANT in clinical studies representing 7860 patient-years of exposure. Of these, 2723 were exposed to OLUMIANT for at least one year. The mean age was 53 years, 79% were female, 66% were white, 3% were black, 26% were Asian, and 5% were other race. Six placebo-controlled studies were integrated (479 patients on OLUMIANT 2 mg once daily, 997 patients on baricitinib 4 mg once daily and 1070 patients on placebo) to evaluate the adverse drug reaction (ADR) profile of OLUMIANT for up to 16 weeks (placebo-controlled) plus extension periods (mean 2.3 years).

During the placebo-controlled period of the studies, treatment emergent adverse events were observed in 57% of patients treated with placebo, 61% of patients treated with OLUMIANT 2 mg, and 64% of patients treated with 4 mg baricitinib. The most common adverse events in the OLUMIANT (baricitinib)-exposed patients up to 16 weeks, reported by >2% of patients and at a higher incidence versus placebo, were as follows: blood CPK increased, hypercholesterolaemia, pharyngitis, nausea, urinary tract infection, hypertension, upper respiratory tract infection, headache, nasopharyngitis, and bronchitis.

The overall incidence rate of SAEs including in a long-term extension study, was higher for the baricitinib 4 mg dose [12.9 per 100 patient-years] than the OLUMIANT 2 mg dose [10.1 per 100 patient-years]. In the baricitinib clinical program, the most common SAEs were as follows (frequency of ≥0.5%, in order of most to least frequent): pneumonia, osteoarthritis, herpes zoster, urinary tract infection, fall, rheumatoid arthritis, and pulmonary embolism.

During the 16 week placebo-controlled treatment period, adverse events leading to discontinuation of treatment were reported in 3% of patients treated with placebo, 4% of patients treated with OLUMIANT 2 mg, and 5% of patients treated with baricitinib 4 mg. The overall incidence rate of adverse events leading to discontinuation of treatment including in a long term extension study was higher with the baricitinib 4 mg dose (7.3 per 100 patient-years) than in the OLUMIANT 2 mg dose (5.0 per 100 patient-years). In the baricitinib clinical program, the most common adverse events leading to discontinuation from treatment were infections. The most common infections (frequency of ≥0.2%) resulting in discontinuation of treatment were herpes zoster, pneumonia, and urinary tract infection.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1 below lists the adverse events (regardless of causality) occurring in ≥1% of patients treated with OLUMIANT at greater frequency versus placebo during the double-blind, placebo-controlled portion of the rheumatoid arthritis studies.

Table 1 - Adverse Events Occurring in ≥1% of OLUMIANT-Treated Patients and in Greater Frequency Than Placebo in Integrated Placebo-Controlled Trials up to 16 Weeks (All Causalities)

System Organ Class/ Adverse Events	Placebo N=1070 n (%)	OLUMIANT 2 mg N=479 n (%)	Baricitinib 4 mg N=997 n (%)
Infections and Infestations			

URTI	39 (3.6)	27 (5.6)	46 (4.6)
UTI	29 (2.7)	17 (3.5)	34 (3.4)
Nasopharyngitis	51 (4.8)	16 (3.3)	53 (5.3)
Bronchitis	30 (2.8)	12 (2.5)	31 (3.1)
Pharyngitis	14 (1.3)	10 (2.1)	23 (2.3)
Sinusitis	12 (1.1)	10 (2.1)	10 (1.0)
Gastroenteritis	9 (0.8)	7 (1.5)	16 (1.6)
Cystitis	9 (0.8)	7 (1.5)	5 (0.5)
Influenza	10 (0.9)	6 (1.3)	18 (1.8)
Rhinitis	3 (0.3)	6 (1.3)	2 (0.2)
Herpes zoster	4 (0.4)	5 (1.0)	14 (1.4)
Gastrointestinal Disorders			
Nausea	17 (1.6)	13 (2.7)	28 (2.8)
Vomiting	6 (0.6)	11 (2.3)	13 (1.3)
Abdominal pain upper	5 (0.5)	10 (2.1)	14 (1.4)
Constipation	15 (1.4)	8 (1.7)	11 (1.1)
Abdominal pain	9 (0.8)	8 (1.7)	8 (0.8)
Investigations			
Blood CPK increased	6 (0.6)	11 (2.3)	35 (3.5)
ALT Increased ≥3 x ULN	10 (0.9)	5 (1.0)	15 (1.5)
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	17 (1.6)	8 (1.7)	17 (1.7)
Muscle Spasms	6 (0.6)	6 (1.3)	8 (0.8)
Nervous System Disorders			
Headache	32 (3.0)	30 (6.3)	38 (3.8)
Dizziness	8 (0.7)	7 (1.5)	14 (1.4)
Metabolism and Nutrition Disorders			
Hypercholesterolemia	14 (1.3)	7 (1.5)	28 (2.8)
Dyslipidemia	5 (0.5)	6 (1.3)	10 (1.0)
Hyperlipidemia	8 (0.7)	5 (1.0)	19 (1.9)
Respiratory, Thoracic, and Mediastinal Disorders			
Cough	17 (1.6)	9 (1.9)	19 (1.9)
Oropharyngeal pain	5 (0.5)	9 (1.9)	12 (1.2)
Skin and Subcutaneous Tissue Disorders			
Rash	8 (0.7)	7 (1.5)	9 (0.9)
General Disorders and Administration Site Conditions			
Fatigue	14 (1.3)	7 (1.5)	11 (1.1)
Pyrexia	8 (0.7)	6 (1.3)	8 (0.8)
Vascular Disorders			
Hypertension	17 (1.6)	16 (3.3)	21 (2.1)
Psychiatric Disorders			
Insomnia	8 (0.7)	5 (1.0)	5 (0.5)
Hepatobiliary Disorders			
Hepatic Function Abnormal	1 (0.1)	5 (1.0)	8 (0.8)

Description of selected Treatment Emergent Adverse Events

Overall Infections: During the 16-week treatment period, infections were reported by 253 patients (82.1 per 100 patient-years) treated with placebo, 139 patients (99.1 per 100 patient-years) treated with OLUMIANT 2 mg, and 298 patients (100.1 per 100 patient-years) treated with baricitinib 4 mg. During 0 to 52 week exposure, infections were reported by 200 patients (59.6 per 100 patients-years) treated with OLUMIANT 2 mg, and 500 patients (55.3 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 per 100 patient-years) treated with placebo, 5 patients (3.6 per 100 patient-years) treated with OLUMIANT 2 mg, and 11 patients (3.7 per 100 patient-years) treated with baricitinib 4 mg. During 0 to 52 week exposure, serious infections were reported in 14 patients (4.2 per 100 patient-years) treated with OLUMIANT 2 mg and 32 patients (3.5 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, Infections).

Tuberculosis: 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. Cases of disseminated tuberculosis were also reported.

Opportunistic Infections: 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, Infections).

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. In the baricitinib clinical trial program, the most common types of malignancies (excluding NMSC) in patients treated with baricitinib were breast, lung, lymphoma, colorectal, prostate, and renal (see WARNINGS AND PRECAUTIONS, Malignancies).

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.

Less Common Clinical Trial Adverse Drug Reactions (<1%)*
Blood and Lymphatic System Disorders: neutropenia <1 x 10^9 cells/L, increased platelet count, low hemoglobin, low hematocrit, low erythrocyte count, MCV high, MCH high, lymphocytes high, high total iron, high ferritin, high transferrin saturation
Ear and Labyrinth Disorders: ear pain
Hepatobiliary Disorders: increased AST ≥3 x ULN, total bilirubin low
Infections and Infestations: oral herpes, pertussis, vulvovaginal candidiasis, tinea pedis
Investigations: increased CPK >5 x ULN, increased albumin
Metabolism and Nutrition Disorders: increased triglycerides ≥5.65 mmol/L, weight increased, decreased blood glucose
Renal and Urinary Disorders: increased creatinine, decreased eGFR
Skin and Subcutaneous Tissue Disorders: acne
Vascular Disorders: deep vein thrombosis, pulmonary embolism
* including Adverse Events with significant imbalance and/or biologic plausibility

Abnormal Hematologic and Clinical Chemistry Findings
Creatine Phosphokinase (CPK) – In controlled clinical trials, 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 U/L and 52 U/L, respectively. Two cases of rhabdomyolysis were reported in rheumatoid arthritis patients in the OLUMIANT clinical trials. In both cases, there were confounding variables, which may have contributed to the rhabdomyolysis.

Lipid Elevations – In controlled studies, dose-dependent, treatment-emergent increases in lipid parameters, including total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol were seen in patients treated with OLUMIANT compared to placebo. Elevations were observed at 12 weeks and remained stable thereafter. Up to 16 weeks, the following rates were observed for OLUMIANT 2 mg versus placebo:

- Increased total cholesterol ≥5.17 mmol/L: 34.7% vs.17.8 %, respectively
- Increased LDL cholesterol ≥3.36 mmol/L: 20.2% vs. 11.6 %, respectively
- Increased HDL cholesterol ≥1.55 mmol/L: 32.9% vs. 12.7 %, respectively
- Increased triglycerides ≥5.65 mmol/L: 0.9% vs. 0.8 %, respectively

In studies which included both doses, a dose-relationship was observed with increased total cholesterol ≥5.17 mmol/L reported in 17.8%, 34.7%, and 48.8% of patients up to 16 weeks in the placebo, OLUMIANT 2 mg, and baricitinib 4 mg groups, respectively. The mean LDL/HDL

ratio remained stable. Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy (see WARNINGS AND PRECAUTIONS, Laboratory Parameters).

Liver Enzyme Elevations – Events of increases in liver enzymes ≥3 x ULN were observed in patients treated with OLUMIANT (see WARNINGS AND PRECAUTIONS, Laboratory Parameters).

- During the 16-week treatment period, ALT elevations ≥3 x 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 ≥3 x 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.

Neutrophils – During the 16-week treatment period, neutrophil counts below 1 x 10^9 cells/L occurred in 0 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 0.5 x 10^9 cells/L observed in any treatment group (see WARNINGS AND PRECAUTIONS, Laboratory Parameters).

Platelets and Thrombocytosis – In controlled studies, dose-dependent, treatment-emergent increases in platelet counts were seen in patients treated with OLUMIANT compared to placebo. Up to 16 weeks, increases in platelet counts above 600 x10^9 cells/L occurred in 2.0% of patients treated with baricitinib 4 mg and 1.1% of patients treated with placebo. In a different dataset which included both doses of baricitinib, increases in platelet counts above 600 x 10^9 cells/L occurred in 2.3% of patients treated with baricitinib 4 mg vs. 1.1% of patients treated with OLUMIANT 2 mg daily (see WARNINGS AND PRECAUTIONS, Laboratory Parameters).

Renal Tests – In controlled clinical trials, dose-related increases in serum creatinine (mean change of 4.1 µmol/L through week 16 with OLUMIANT 2 mg) and urea nitrogen, and decreases in eGFR and creatinine clearance were observed in clinical trials with OLUMIANT (see WARNINGS AND PRECAUTIONS, Renal Function, and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Overview

In vitro assessment of interactions

The metabolism of baricitinib is primarily mediated by CYP3A4. In vitro, baricitinib is a cytochrome P450 enzyme (CYP)3A4 substrate. In vitro, baricitinib did not significantly inhibit nor induce the activity of cytochrome P450 enzymes (CYPs 3A, 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6).

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 vitro studies suggest that baricitinib is a substrate for OAT3, Pgp, BCRP and MATE2-K.

Clinical drug-drug interaction potential exists with strong OAT3 inhibitors and immunosuppressants, other JAK Inhibitors or biologic DMARDs (see DOSAGE AND ADMINISTRATION, Dose Modifications Due to Drug Interactions).

Drug-Drug Interactions

Pharmacokinetic interactions

Effect of baricitinib on the pharmacokinetics of other drugs

Cytochrome P450 enzymes – 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.

Transporters – In clinical pharmacology studies, there were no clinically meaningful effects on the pharmacokinetics of digoxin (Pgp substrate) or methotrexate (substrate of several transporters) when co-administered with baricitinib.

The drugs listed in Table 2 and Figure 1 (forest plot) are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

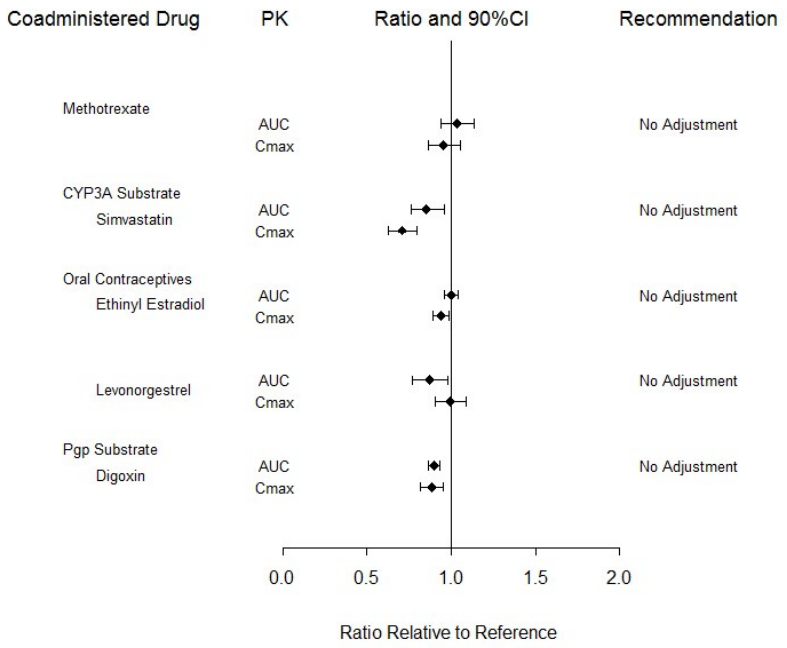
Table 2 – Established or Potential Drug-Drug Interactions – Effect of baricitinib on the pharmacokinetics of other drugs

Co-administered Drug	Dose of Co-administered Drug	Dose of Baricitinib	Reference[a]	Effect Geometric Mean ratio (Ratio with/without co-administered drug) – No effect = 1.0			Clinical comment
				Measured Analyte	AUC (90% CI)	C_{max} (90% CI)	
Methotrexate	7.5 mg – 25 mg weekly, multiple dose, RA patients	10 mg, multiple dose	CT	Methotrexate	1.03[b] (0.94 - 1.13)	0.95 (0.86 - 1.05)	No dosage adjustment of methotrexate is required when co-administered with OLUMIANT.
Simvastatin	40 mg, single dose, healthy subjects	10 mg, multiple dose	CT	Simvastatin	0.85[b] (0.76 - 0.96)	0.71 (0.63 - 0.80)	No dosage adjustment of simvastatin is required when co-administered

				Simvastatin acid (metabolite)	0.84 [b] (0.75 - 0.94)	0.88 (0.79 – 0.98)	with OLUMIANT.
Microgynon (Ethinyl estradiol and levonorgestrel)	30 µg, single dose (ethinyl estradiol) and 150 µg, single dose (levonorgestrel), healthy subjects	10 mg, multiple dose	CT	Ethinyl estradiol Levonorgestrel	1.00 [b] (0.96 - 1.04) 0.87 [b] (0.77 - 0.98)	0.94 (0.89 - 0.99) 1.00 (0.91 – 1.09)	No dosage adjustment of ethinyl estradiol and levonorgestrel is required when co-administered with OLUMIANT.
Digoxin	0.5 mg BID (loading dose on Day 1), then 0.25 mg QD, healthy subjects	10 mg, multiple dose	CT	Digoxin	0.90 [c] (0.87 - 0.94)	0.88 (0.82 - 0.95)	No dosage adjustment of digoxin is required when co-administered with OLUMIANT.

[a] Legend: C = Case Study; CT = Clinical Trial; T = Theoretical (based on simulations); [b] AUC = $AUC_{0-\infty}$; [c] $AUC_{0-\tau}$

Figure 1: Impact of Baricitinib on the Pharmacokinetics of Other Drugs[a]



[a] Reference group is administration of concomitant drug alone.

Effect of other drugs on the pharmacokinetics of baricitinib

Strong OAT3 Inhibitors – In a clinical pharmacology study, probenecid administration (strong OAT3 inhibitor) resulted in an approximately 2-fold increase in baricitinib $AUC_{0-\infty}$ and a ~70%

decrease in renal clearance of baricitinib with no effect on C_{max} and t_{max}. OLUMIANT is not recommended in patients taking OAT3 inhibitors with a strong inhibition potential, such as probenecid (see DOSAGE AND ADMINISTRATION, Dose Modifications Due to Drug Interactions).

Immunosuppressants, Other JAK Inhibitors or Biologic DMARDs – Combined use of OLUMIANT with other JAK inhibitors or biologic DMARDs has not been studied in rheumatoid arthritis patients and is not recommended (see DOSAGE AND ADMINISTRATION).

In clinical pharmacology studies, there was no clinically meaningful effect on the PK of baricitinib when co-administered with cyclosporine (Pgp and BCRP inhibitor). However, there is a risk of added immunosuppression when OLUMIANT is co-administered with potent immunosuppressive drugs (e.g., tacrolimus, cyclosporine, azathioprine). The combined use with these potent immunosuppressives has not been studied in rheumatoid arthritis patients and is not recommended (see DOSAGE AND ADMINISTRATION).

Cytochrome P450 enzymes – In clinical pharmacology studies, there was no clinically meaningful 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).

Transporters – Co-administration with methotrexate (substrate of several transporters) did not have a clinically meaningful effect on the PK of baricitinib. Simulations with diclofenac and ibuprofen (OAT3 inhibitors with less inhibition potential) predicted minimal effect on baricitinib exposure.

The drugs listed in Table 3 and Figure 2 (forest plot) are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 - Established or Potential Drug-Drug Interactions – Effect of co-administered Drugs on the pharmacokinetics of Baricitinib

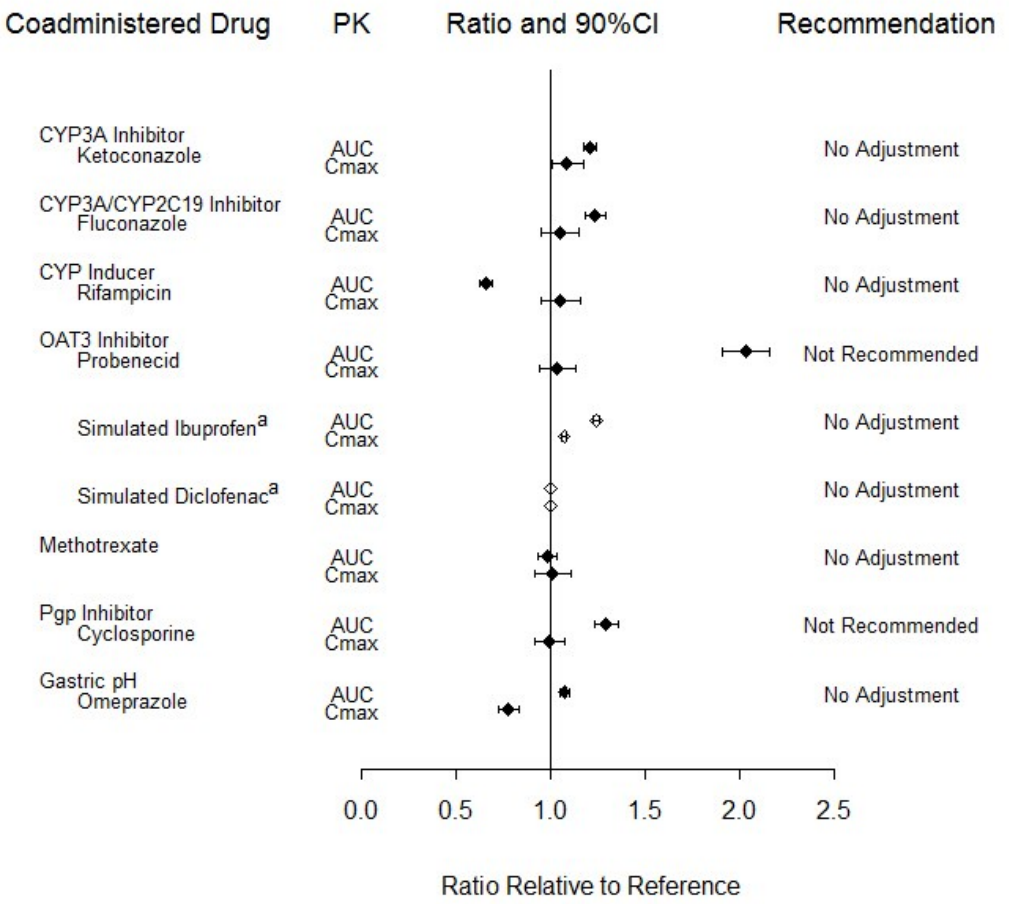
Co-administered Drug	Dose of Co-administered Drug	Dose of Baricitinib	Reference[a]	Effect Geometric Mean ratio (Ratio with/without co-administered drug) - No effect =1.0			Clinical comment
				Measured Analyte	AUC (90% CI)	C_{max} (90% CI)	

Probenecid	1000 mg twice daily, multiple dose, healthy subjects	4 mg, single dose	CT	Baricitinib	2.03[b] (1.91 - 2.16)	1.03 (0.94 - 1.13)	OLUMIANT is not recommended in patients taking OAT3 inhibitors with a strong inhibition potential, such as probenecid.
Cyclosporine	600 mg, single dose, healthy subjects	4 mg, single dose	CT	Baricitinib	1.29[b] (1.23 - 1.36)	0.99 (0.91 - 1.07)	There is a risk of added immunosuppression when OLUMIANT is co-administered with potent immunosuppressive drugs (e.g., tacrolimus, cyclosporine, azathioprine). The combined use with these potent immunosuppressives has not been studied in rheumatoid arthritis patients and is not recommended.
Ketoconazole	400 mg, multiple dose, healthy subjects	10 mg, single dose	CT	Baricitinib	1.21[b] (1.17 - 1.24)	1.08 (1.01 - 1.17)	No dosage adjustment of OLUMIANT is required when co-administered with ketoconazole.
Fluconazole	200 mg, multiple dose, healthy subjects	10 mg, single dose	CT	Baricitinib	1.23[b] (1.18 - 1.29)	1.05 (0.95 - 1.15)	No dosage adjustment of OLUMIANT is required when co-administered with fluconazole.
Rifampicin	600 mg, multiple dose, healthy subjects	10 mg, single dose	CT	Baricitinib	0.66[b] (0.62 - 0.69)	1.05 (0.95 - 1.16)	No dosage adjustment of OLUMIANT is required when co-administered with rifampicin.

Simulated Ibuprofen	400 mg and 800 mg, multiple dose, healthy subjects	4 mg, multiple dose	T	Baricitinib	1.24[b] (1.22 - 1.26)	1.07 (1.06 - 1.08)	No dosage adjustment of OLUMIANT is required when co-administered with ibuprofen.
Simulated Diclofenac	50 mg and 100 mg, multiple dose, healthy subjects	4 mg, multiple dose	T	Baricitinib	1.00[b] (1.00 - 1.00)	1.00 (1.00 - 1.00)	No dosage adjustment of OLUMIANT is required when co-administered with diclofenac.
Methotrexate	7.5 mg – 25 mg weekly, multiple dose, RA patients	10 mg, multiple dose	CT	Baricitinib	0.98[c] (0.93 - 1.03)	1.01 (0.92 - 1.11)	No dosage adjustment of OLUMIANT is required when co-administered with methotrexate.
Omeprazole	40 mg, multiple dose, healthy subjects	10 mg, single dose	CT	Baricitinib	1.07[b] (1.05 - 1.10)	0.77 (0.72 - 0.83)	No dosage adjustment of OLUMIANT is required when co-administered with omeprazole.

[a] Legend: C = Case Study; CT = Clinical Trial; T = Theoretical (based on simulations); [b] AUC = $AUC_{0-\infty}$; [c] $AUC_{0-\tau}$

Figure 2: Impact of Other Drugs on the Pharmacokinetics of Baricitinib[b]



[a] Values are based on simulated studies.
[b] Reference group is administration of baricitinib alone.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interaction with herbal products has not been established.

Drug-Laboratory Interactions
Interaction with laboratory tests has not been established.

Drug-Lifestyle Interactions
No formal studies have been conducted on the effects on the ability to drive and use machines.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Immunosuppressants, Other JAK Inhibitors or Biologic DMARDs: There is a risk of additive immunosuppression when OLUMIANT is coadministered with potent immunosuppressant drugs (e.g. azathioprine, tacrolimus, cyclosporine). Combined use of OLUMIANT with potent immunosuppressants, other JAK inhibitors or biologic DMARDs has not been studied in rheumatoid arthritis patients and is not recommended.

Dose Modification due to Serious Infections, Anemia, neutropenia and lymphopenia: OLUMIANT should not be initiated in patients with an absolute lymphocyte count (ALC) <0.5 x 10^9 cells/L, absolute neutrophil count (ANC) <1 x 10^9 cells/L, or hemoglobin levels <80 g/L (see WARNINGS AND PRECAUTIONS, Laboratory Parameters, and ADVERSE REACTIONS).

Avoid use of OLUMIANT in patients with active serious infection, including localized infections (see WARNINGS AND PRECAUTIONS, Infections).

Prior to initiating OLUMIANT, test patients for latent tuberculosis (TB). Treatment for latent infection should be initiated prior to OLUMIANT use (see WARNINGS AND PRECAUTIONS, Infections).

Recommended Dose and Dosage Adjustment

Adults: The recommended dose of OLUMIANT is 2 mg once daily in combination with methotrexate.

Monotherapy may be considered in cases of intolerance to methotrexate.

OLUMIANT may be given with or without regard to food.

Dose Modifications Due to Drug Interactions: OLUMIANT is not recommended in patients taking OAT3 inhibitors with a strong inhibition potential, such as probenecid (see DRUG INTERACTIONS).

Dosing in Special Populations:

Patients with Renal Impairment: OLUMIANT is not recommended for use in patients with an estimated GFR of less than 60 mL/min/1.73 m^2 (moderate to severe renal impairment and ESRD) (see WARNINGS AND PRECAUTIONS, and ACTION AND CLINICAL PHARMACOLOGY). No dose adjustment is necessary in patients with mild renal impairment.

Patients with Hepatic Impairment: OLUMIANT is not recommended for use in patients with severe hepatic impairment. No dose adjustment is necessary in patients with mild or moderate hepatic impairment (see WARNINGS AND PRECAUTIONS, Hepatic, and ACTION AND CLINICAL PHARMACOLOGY).

Geriatrics (≥65 years of age): No dosage adjustment is required in patients aged 65 years and older (see WARNINGS and PRECAUTIONS, Special Populations, and ACTION AND CLINICAL PHARMACOLOGY).

Pediatrics (<18 years of age): The safety and effectiveness of OLUMIANT in pediatric patients have not been established. Therefore, OLUMIANT should not be used in this patient population (see WARNINGS AND PRECAUTIONS, Special Populations).

Missed Dose
If a scheduled dose of OLUMIANT is missed, it should be taken as soon as possible. Patients should not take more than 1 tablet per day.

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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Janus kinases (JAKs) are enzymes that transduce intracellular signals from cell surface receptors for a number of cytokines and growth factors involved in hematopoiesis, inflammation and immune function. Within the intracellular signaling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs), which modulate intracellular activity including gene expression. Baricitinib modulates these signaling pathways by inhibiting JAK, thereby reducing the phosphorylation and activation of STATs. JAK enzymes transmit cytokine signaling through pairing of JAKs (e.g., JAK1/JAK3, JAK1/JAK2, JAK1/TYK2, JAK2/JAK2).

Baricitinib is a selective and reversible inhibitor of JAK over other kinases in the human genome. In isolated enzyme assays, baricitinib had greater inhibitory potency at JAK1, JAK2, and TYK2 relative to JAK3 with IC50 values of 5.9, 5.7, 53 and >400 nM, respectively for JAK1, JAK2, TYK2 and JAK3. In cellular assays, baricitinib inhibited JAK1/JAK2 and JAK1/TYK2 signaling by pro-inflammatory cytokines IL-6 and IL-23 at IC50 values of ~40 to 50 nM but also inhibited JAK1/JAK3 signaling by IL-2 in the nanomolar range. The effects of baricitinib in vitro are consistent with attenuation of pro-inflammatory response as well as modulation of lymphocyte activation, proliferation, and cytokine production.

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 to 2 hours 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.

Lymphocytes – Mean absolute lymphocyte count increased by 1 week after starting treatment with OLUMIANT, returned to baseline by week 24 and then remained stable through at least 104 weeks. For most patients, changes in lymphocyte count occurred within the normal reference range.

Natural killer cells – Treatment with baricitinib 4mg was associated with an initial increase in natural killer cell counts at Week 4 followed by a decrease to below baseline at Week 12, which gradually returned to near baseline levels.

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
In a randomised, placebo- and positive-controlled, 3-period crossover ECG assessment study in healthy subjects (N=53), a single supratherapeutic 40 mg dose of OLUMIANT was not associated with any treatment-related pattern of effects on the QTc interval, the QRS duration, or the PR interval.

Pharmacokinetics
Following oral administration of OLUMIANT 1 mg to 20 mg in healthy volunteers, peak plasma concentrations (t_{max}) are reached approximately at 1 hour. Steady-state concentrations are achieved in 2 to 3 days with minimal accumulation (11% and 15% based on C_{max} and AUC, respectively) after once-daily administration. A dose-proportional increase in systemic exposure was observed in the dose range of 1 mg to 30 mg (single daily dose) and 2 mg to 20 mg (multiple daily dose). The pharmacokinetics of baricitinib do not change over time.

At steady state after multiple 2-mg once-daily dosing in patients with RA, the C_{max} of baricitinib was 24.4 ng/mL, and the mean area under the concentration-time curve at a dosing interval at steady state was 228.4 ng*hr/mL based on the Phase 3 clinical study RA-BEACON. The CL/F in patients with RA is approximately 50% lower than that in healthy subjects. The population pharmacokinetic parameters estimates from Study RA-BEACON are similar to those from the other Phase 2 and Phase 3 clinical studies.

Table 4 - Summary of OLUMIANT's Pharmacokinetic Parameters after Repeated Oral Administration of 2 mg QD in Humans[a]

	$C_{max,\ ss}$ (ng/mL)	$t_{½}$ (h)	$AUC_{\tau,\ ss}$ (ng*hr/mL)	Clearance (L/h)	Volume of distribution (L)
Healthy Volunteers[b]	17.2	8.5	118.1	17.6	216
Rheumatoid Arthritis Patients[c]	24.4	12.5	228.4	9.0	131.3

[a] Legend: $C_{max,\ ss}$ = maximum observed drug concentration; $t_{1/2}$ = terminal elimination half-life; $AUC_{\tau,\ ss}$ = area under the concentration-time curve during one dosing interval at steady state; [b] Study JADE; [c] the $t_{1/2}$ estimate is from population PK analysis based on combined phase 2 and phase 3 studies; other values are from population PK analysis based on Study RA-BEACON.

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.

Metabolism: Approximately 6% of the orally administered baricitinib dose is identified as oxidative 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: 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%) with identified metabolites in urine and feces accounting for approximately 6%. Renal elimination is the principal mechanism for baricitinib's clearance through filtration and active secretion via OAT3, Pgp, BCRP and MATE2-K from in vitro studies.

Special Populations and Conditions
Pediatrics: The safety and efficacy of OLUMIANT in children and adolescents aged 0 to 18 years have not yet been established.

Geriatrics: No dose adjustment is required for patients aged ≥65 years (see DOSAGE AND ADMINISTRATION, Dosing in Special Populations, and Figure 3). Age did not have a clinically relevant effect on the PK (AUC and C_{max}) of baricitinib. However, clinical experience in patients ≥75 years is very limited and caution should be used when treating the elderly with

OLUMIANT as the greater sensitivity of some older individuals cannot be ruled out (see WARNINGS AND PRECAUTIONS, Special Populations).

Gender: No dose adjustment is necessary based on gender (see Figure 3). Based on population pharmacokinetic analysis, women were estimated to have 7% and 16% difference in AUC and C_{max}, respectively, compared to men after accounting for differences in renal function. These values of mean effects of AUC and C_{max} were generally within the inter-subject PK variability (approximately 41% for AUC and 22% for C_{max}) of baricitinib and are not considered to be clinically relevant.

Race: No dose adjustment is necessary based on race (see Figure 3). Based on population pharmacokinetic analysis, Blacks, Hispanics and Asians were estimated to have 16%, 10%, and 10% difference in AUC, and 9%, 1%, and 15% in C_{max}, respectively, compared to Caucasians. These values of mean effects of AUC and C_{max} were generally within the inter-subject PK variability (approximately 41% for AUC and 22% for C_{max}) of baricitinib and are not considered to be clinically relevant.

Body weight: No dose adjustment is necessary based on body weight (see Figure 3). Based on population PK analysis, patients at the extremes of the body weight of 50 and 100 kg were estimated to have less than 14% and 20% difference in the AUC and C_{max}, respectively, relative to those at the median weight of 70 kg, after accounting for differences in renal function. These values of mean effects of AUC and C_{max} were generally within the inter-subject PK variability (approximately 41% for AUC and 22% for C_{max}) of baricitinib and are not considered to be clinically relevant.

Hepatic Insufficiency: 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, Dosing in Special Populations, and Figure 3).

In a Phase I, open-label study conducted in subjects with moderate hepatic impairment, baricitinib systemic exposure ($AUC_{0-\infty}$) and C_{max} increased by 1.19- and 1.08-fold respectively in subjects with moderate hepatic impairment (Child-Pugh B classification), compared to subjects with normal hepatic function.

Renal Insufficiency: Renal function was found to significantly affect baricitinib exposure (see Figure 3). OLUMIANT is not recommended for use in patients with moderate renal impairment, severe renal impairment or ESRD (estimated GFR of less than 60 mL/min/1.73 m^2). (See WARNINGS AND PRECAUTIONS, Renal, DOSAGE AND ADMINISTRATION, Dosing in Special Populations, and Figure 3). No dose adjustment is necessary in patients with mild renal impairment.

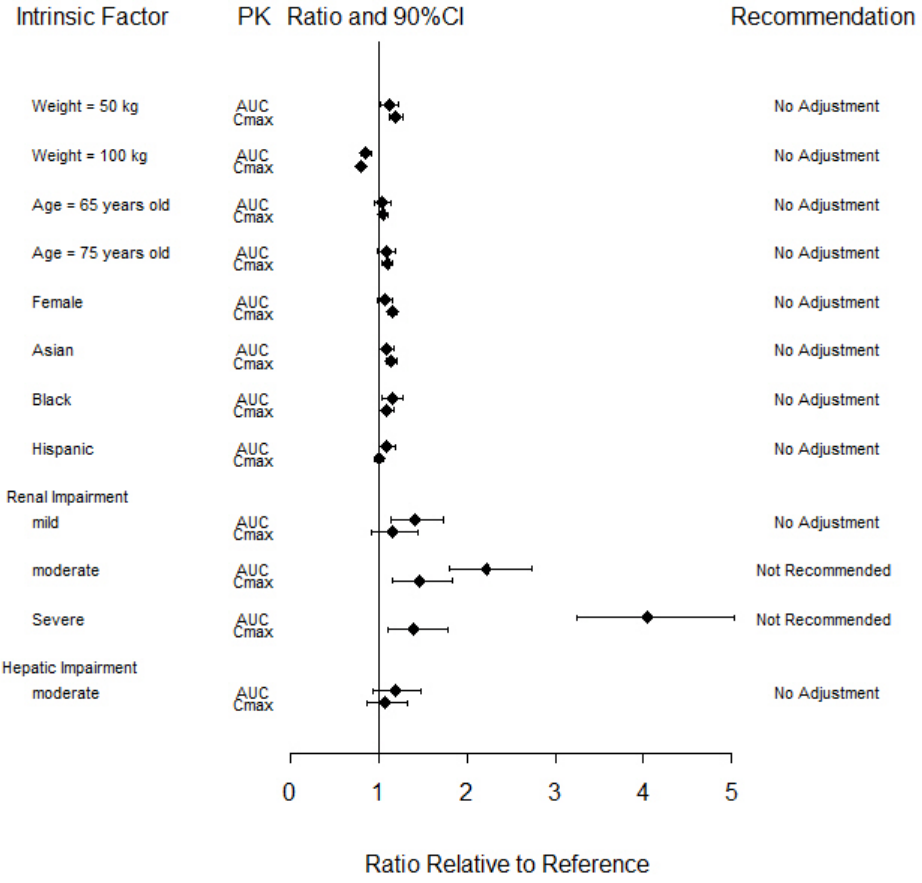
In a Phase I, open label study conducted in subjects with renal impairment, baricitinib systemic exposure ($AUC_{0-\infty}$) increased by 1.41-, 2.22-, 4.05- and 2.41-fold for mild, moderate, severe, and ESRD (with hemodialysis) renal impairment sub-groups, respectively, compared to subjects with

normal renal function. The corresponding values for increase in C_{max} were 1.16-, 1.46-, 1.40- and 0.88-fold, respectively.

Genetic polymorphism: No studies have been conducted specifically to evaluate the effects of genetic polymorphism on the pharmacokinetics of baricitinib.

The impact of intrinsic factors on the pharmacokinetics of baricitinib and the dosing recommendations are summarized in Figure 3.

Figure 3: Impact of Intrinsic Factors on Baricitinib Pharmacokinetics[a]



[a] 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.

[b] 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.

STORAGE AND STABILITY

Store at room temperature between 15° - 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each tablet contains a recessed area on each face of the tablet surface and is 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.

Nonmedicinal ingredients include croscarmellose sodium, magnesium stearate, mannitol, and microcrystalline cellulose. The color coatings contain ferric oxide, lecithin (soya), polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

OLUMIANT is available as bottles containing 30 or 90 tablets and in blister packages of 14 (1x14) or 28 (2x14). Not all pack sizes and presentations may be marketed.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

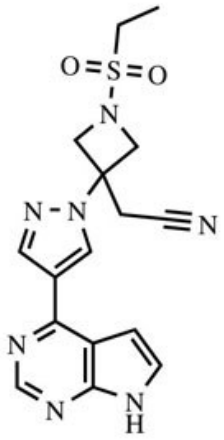
Drug Substance

Proper name: baricitinib

Chemical name: {1-(ethylsulfonyl)-3-[4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-3-yl}acetonitrile

Molecular formula and molecular mass: $C_{16}H_{17}N_7O_2S$ and a molecular weight of 371.42.

Structural formula:



Crystal form: Anhydrous crystalline, Form I

Physicochemical properties:

Baricitinib is a white to practically white to light pink powder. It is practically insoluble in water, pH 4.1 USP acetate buffer, pH 6.0 USP phosphate buffer, and pH 7.6 USP phosphate buffer. It is slightly soluble in 0.1 N HCl and 0.01 N HCl.

CLINICAL TRIALS

The efficacy and safety of OLUMIANT were assessed in four confirmatory Phase 3 trials in patients ≥18 years with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Two of the four Phase 3 confirmatory studies assessed the efficacy and safety of OLUMIANT 2 mg once daily. Although other doses have been studied, the recommended dose of OLUMIANT is 2 mg once daily.

OLUMIANT (baricitinib) has been studied in patients with moderately to severely active rheumatoid arthritis who had an inadequate response or intolerance to conventional DMARDs (cDMARDs-IR; Study III, RA-BUILD) and in patients who had an inadequate response or intolerance to one or more TNF inhibitor therapies with or without other biologic DMARDs (TNFi-IR; Study IV, RA-BEACON). Patients received OLUMIANT 2 mg or baricitinib 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.

Both studies demonstrated statistically significant effects of OLUMIANT 2 mg compared to placebo for the proportion of patients exhibiting a positive ACR20 response, as well as a statistically significant improvement across several efficacy measures. Results at Week 24 were similar to those at Week 12.

Study Demographics and Trial Design

Table 5 - Summary of Patient Demographics for Clinical Trials in Specific Indication[a]

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age years (Range)	Gender (% M/F)	Mean disease duration in years (Range)[b]
cDMARD-IR						
RA-BUILD (Study III)	Randomised, double-blind, double-dummy, parallel group, placebo-controlled, multicentre	Baricitinib 2 mg or 4 mg vs. placebo Tablets, orally, once daily Main treatment period: 24 weeks	Baricitinib 2 mg: 229 Baricitinib 4 mg: 227 Placebo: 228	51.8 (20-82)	18.1/81.9	6.3 (0.07-52.8)
TNFi-IR						
RA-BEACON (Study IV)	Randomised, double-blind, double-dummy,	Baricitinib 2 mg or 4 mg vs. placebo Tablets, orally,	Baricitinib 2 mg: 174 Baricitinib 4 mg: 177	55.7 (21-82)	18.2/81.8	12.5 (0.62-50.7)

	parallel group, placebo-controlled, multicentre	once daily Main treatment period: 24 weeks	Placebo: 176			

[a] Abbreviations: cDMARD-IR = conventional disease-modifying anti-rheumatic drugs-inadequate response; TNFi-IR = tumor necrosis factor-alpha inhibitors-inadequate response; M = male; F = female.
[b] Years since diagnosis.

Clinical Response

The percentages of OLUMIANT-treated patients achieving ACR20, ACR50, and ACR70 responses, clinical remission as measured by Simplified Disease Activity Index (SDAI) ≤3.3 and Disease Activity Score (DAS28-hsCRP) <2.6 in Studies III (RA-BUILD) and IV (RA-BEACON) are shown in Tables 6 and 7.

In RA-BUILD and RA-BEACON, patients treated with OLUMIANT 2 mg once daily had statistically significantly higher ACR20, ACR50 and ACR70 response rates at 12 weeks compared to placebo-treated patients (Table 6).

In both studies, higher ACR20 response rates (Figures 4 and 5) were observed as early as one week with OLUMIANT 2 mg versus placebo.

Patients treated with OLUMIANT 2 mg had higher rates of clinical remission and DAS28-hsCRP<2.6 versus placebo-treated patients at Week 12 (Table 7).

Table 6 – Proportion of Patients with an ACR Response

	Percent of Patients			
	cDMARD-IR		**TNFi-IR**	
	Study III (RA-BUILD)		**Study IV (RA-BEACON)**	
	Placebo + cDMARDs	**OLUMIANT 2 mg/day + cDMARDs (95% CI)[a]**	**Placebo + cDMARDs**	**OLUMIANT 2 mg/day + cDMARDs (95% CI)[a]**
N	**228**	**229**	**176**	**174**
ACR 20				
Week 12	39%	66%[b,c] (17.6, 35.3)	27%	49%[b,d] (11.7, 31.5)
Week 24[d]	42%	61%[b] (10.0, 28.0)	27%	45%[b] (7.7, 27.4)
ACR 50[d]				
Week 12	13%	34%[b] (13.4, 28.4)	8%	20%[b] (5.0, 19.3)

Week 24	21%	41%[b] (11.7, 28.3)	13%	23%[b] (1.9, 17.9)
ACR 70[d]				
Week 12	3%	18%[b] (9.4, 20.3)	2%	13%[b] (5.0, 15.8)
Week 24	8%	25%[b] (10.8, 24.1)	3%	13%[b] (4.1, 15.5)

Proportions of responders at each time point base on those initially randomized to treatment (N). Patients who discontinued or received rescue therapy were considered as non-responders.

[a] 95% confidence interval for the difference in response rate between OLUMIANT treatment and placebo.

[b] p≤0.05 for the comparison between OLUMIANT treatment and placebo.

[c] Type I error controlled.

[d] Type I error not controlled.

Figures 4 and 5: Percent of Patients Achieving ACR20

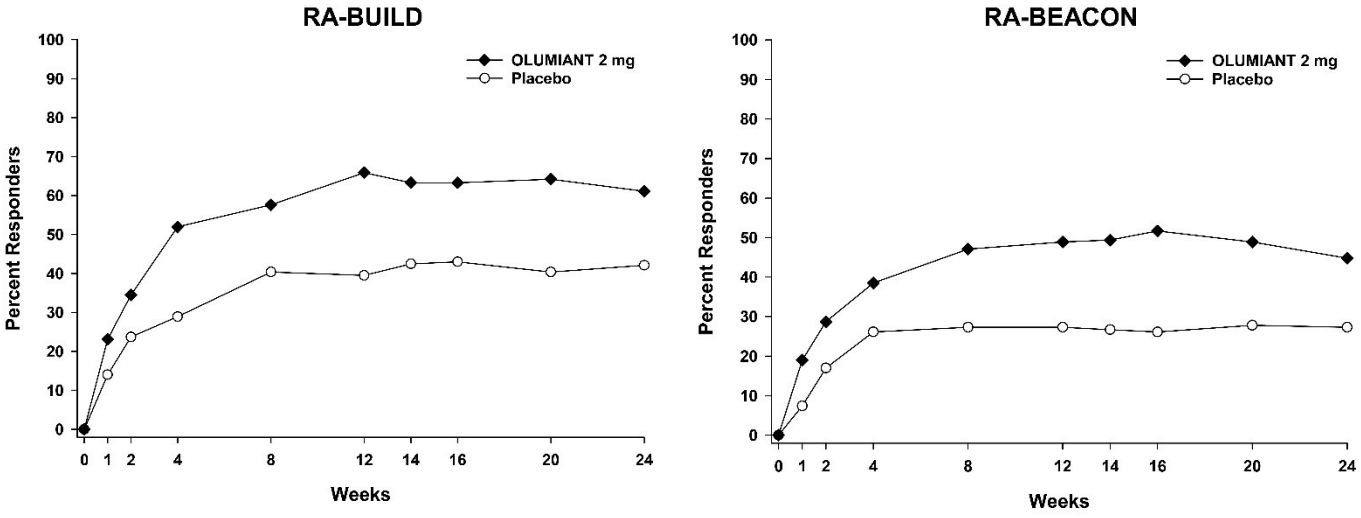


Table 7 - Clinical Remission (SDAI ≤3.3) and DAS28-hsCRP <2.6

	Percent of Patients			
	cDMARD-IR		**TNFi-IR**	
	Study III (RA-BUILD)		**Study IV (RA-BEACON)**	
	Placebo + cDMARDs	**OLUMIANT 2 mg/day + cDMARDs (95% CI)[a]**	**Placebo + cDMARDs**	**OLUMIANT 2 mg/day + cDMARDs (95% CI)[a]**
N	**228**	**229**	**176**	**174**
SDAI ≤3.3[b]				

Week 12	1%	9%[c, d, f] (4.4, 12.2)	2%	2%[d, g] (-2.3, 3.5)
Week 24[g]	4%	17%[c, d] (7.2, 18.1)	2%	5%[d] (-1.5, 6.1)
DAS28-hsCRP <2.6[e, g]				
Week 12	9%	26%[c, d] (10.2, 23.7)	4%	11%[c,d] (1.5, 12.4)
Week 24	11%	31%[c, d] (12.9, 27.2)	6%	11%[d] (-1.2, 10.5)

[a] 95% confidence interval for the difference in response rate between OLUMIANT treatment and placebo.
[b] Simplified Disease Activity Index.
[c] p≤0.05 for the comparison between OLUMIANT treatment and placebo.
[d] p≤0.05 for the comparison of mean changes from baseline in the index score between OLUMIANT treatment and placebo.
[e] Disease Activity Score 28-high sensitivity C-reactive protein.
[f] Type I error controlled.
[g] Type I error not controlled.

The effect of OLUMIANT treatment on the components of the ACR response criteria for RA-BUILD and RA-BEACON are shown in Table 8.

Table 8 - Components of ACR Response at Weeks 12 and 24[a]

	cDMARD-IR		**TNFi-IR**	
	Study III (RA-BUILD)		**Study IV (RA-BEACON)**	
	Placebo + cDMARDs	**OLUMIANT 2 mg/day + cDMARDs**	**Placebo + cDMARDs**	**OLUMIANT 2 mg/day + cDMARDs**
N	**228**	**229**	**176**	**174**
Number of Tender Joints (0-68)				
Baseline	24 (15)	24 (14)	28 (16)	31 (16)
Week 12	15 (14)	11 (13)	20 (16)	19 (18)
Week 24	14 (15)	10 (12)	19 (17)	19 (19)
Number of Swollen Joints (0-66)				
Baseline	13 (7)	14 (9)	17 (11)	19 (12)
Week 12	8 (8)	5 (6)	12 (10)	10 (12)
Week 24	8 (8)	5 (7)	12 (11)	11 (12)
Pain[b]				
Baseline	57 (23)	60 (21)	65 (19)	62 (22)
Week 12	43 (24)	34 (25)	55 (25)	46 (28)
Week 24	39 (24)	32 (25)	54 (26)	43 (28)
Patient Global Assessment[b]				
Baseline	60 (21)	62 (20)	66 (19)	67 (19)

Week 12	44 (23)	36 (25)	56 (25)	46 (26)
Week 24	42 (23)	34 (24)	56 (25)	45 (27)
Physician Global Assessment[b]				
Baseline	62 (17)	64 (17)	67 (19)	67 (17)
Week 12	41 (24)	33 (22)	50 (26)	36 (24)
Week 24	37 (26)	28 (23)	46 (29)	37 (27)
Disability Index (HAQ-DI)[c]				
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)
Week 24	1.14 (0.66)	0.90 (0.69)	1.59 (0.67)	1.29 (0.74)
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)
Week 24	15.2 (19.3)	8.4 (15.5)	21.7 (28.7)	13.4 (19.7)

[a] Data shown are mean (standard deviation).
[b] Visual analog scale: 0 = best, 100 = worst.
[c] 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 and Health-Related Outcomes
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 function compared to placebo at Week 24. The mean difference (95% CI) from placebo in HAQ-DI change from baseline at Week 24 is shown in Table 9.

Table 9 – Mean Change from Baseline in HAQ-DI at Week 24

	Study III RA-BUILD		**Study IV RA-BEACON**	
	Placebo + cDMARDs	**OLUMIANT 2 mg/ day + cDMARDs**	**Placebo + cDMARDs**	**OLUMIANT 2 mg/ day + cDMARDs**
N	**228**	**229**	**176**	**174**
HAQ-DI				
LS Mean	-0.38	-0.62	-0.15	-0.38
Difference from placebo (95% CI)	-	-0.24[a, b] (-0.35, -0.14)	-	-0.23[a, c] (-0.35, -0.12)
HAQ-DI responder rates[d]	37.3%	58.1%	23.9%	41.4%

[a] $p \leq 0.05$ for the comparison between OLUMIANT treatment and placebo.
[b] Type I error controlled.
[c] Type I error not controlled.
[d] Percentage of patients with an improvement from baseline ≥0.30.

General health status was assessed by the Short Form health survey (SF-36). In RA-BUILD and RA-BEACON, 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.

DETAILED PHARMACOLOGY

Mechanism of Action

Janus kinases (JAKs) are enzymes that transduce intracellular signals from cell surface receptors for a number of cytokines and growth factors involved in hematopoiesis, inflammation and immune function. Within the intracellular signaling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs), which modulate intracellular activity including gene expression. Baricitinib modulates these signaling pathways by inhibiting JAK, thereby reducing the phosphorylation and activation of STATs. JAK enzymes transmit cytokine signaling through pairing of JAKs (e.g., JAK1/JAK3, JAK1/JAK2, JAK1/TYK2, JAK2/JAK2).

Baricitinib is a selective and reversible inhibitor of JAK. In isolated enzyme assays, baricitinib inhibited the activities of JAK1, JAK2, TYK2 and JAK3 with IC50 values of 5.9, 5.7, 53 and >400 nM, respectively. In cellular assays, baricitinib inhibited JAK1/JAK2 and JAK1/TYK2 signaling by pro-inflammatory cytokines IL-6 and IL-23 at IC50 values of ~40 to 50 nM, but also inhibited JAK1/JAK3 signaling by IL-2 in the nanomolar range. Inhibition of IL-6 induced STAT3 proliferation in whole blood was used to assess effects in different species and as an ex vivo marker for pharmacological activity. Baricitinib was pharmacologically active in rats and dogs; the IC50 was 104, 49 and 128 nM in human, dog and rat, respectively. Samples of blood from baricitinib treated rats with adjuvant-induced arthritis and healthy dogs showed dose dependent inhibition of STAT3 phosphorylation, highest at the first sampling point (1h) after gavage dosing, decreasing at 4 h, and with no effect in samples collected 24 h post dose in the rat. Preclinical efficacy of baricitinib was determined in rodent models with established disease. Oral daily dosing of baricitinib for 14 days resulted in improvement of clinical and histopathological scores/severity of disease, as well as reduced the expression of pathogenic cytokines.

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 to 2 hours 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.

Lymphocytes – Mean absolute lymphocyte count increased by 1 week after starting treatment with OLUMIANT, returned to baseline by week 24 and then remained stable through at least 104 weeks. For most patients, changes in lymphocyte count 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.

Pharmacokinetics
Following oral administration of OLUMIANT, peak plasma concentrations are reached within 1 hour. Elimination half-life in patients with RA is approximately 13 hours. Steady-state concentrations are achieved in 2 to 3 days with minimal accumulation after once-daily administration.

A dose-proportional increase in systemic exposure was observed in the therapeutic dose range. Over the single dose range of 1- to 30-mg in healthy subjects, the mean baricitinib C_{max} and $AUC_{0-\infty}$ values increased approximately proportional to dose. Ratios (90% CI) for dose-normalized C_{max} and $AUC_{0-\infty}$ were 1.02 (0.89, 1.18), and 1.13 (1.07, 1.20), respectively. The pharmacokinetics of baricitinib do not change over time.

TOXICOLOGY

Single Dose and Repeat Dose Toxicity
The single-dose oral toxicity of baricitinib was evaluated in CD-1 mice, Sprague Dawley rats, and beagle dogs. In general, baricitinib has low single-dose oral toxicity. No mortality was observed at the maximum doses tested in mice (1200 mg/kg), rats (600 mg/kg), and dogs (40 mg/kg). Clinical findings of emesis and decreased activity were observed in individual dogs given ≥5 mg/kg baricitinib.

The toxicologic and toxicokinetic profiles of baricitinib were characterized in oral studies of up to 3 months in mice, 6 months in rats and 9 months in dogs. The pivotal rat and dog studies included a recovery phase to assess reversibility of any adverse effects. Overall, the major cell types affected by JAK inhibition in the nonclinical safety studies were decreases in lymphocytes, leukocytes, T cells, eosinophils, erythrocytes, and reticulocytes. Associated with these changes were generalized lymphoid depletion and bone marrow hypocellularity with rats more affected than dogs. In mice, rats, and dogs, baricitinib exposures generally increased with increasing dose, but were not consistently dose proportional.

Other potentially treatment-related findings in the 39-week dog study consisted of liver toxicity, prostate atrophy and reduced prostate weight at 3 and 6/9 mg/kg/day, without any effect on the testes, and gliosis and perivascular mononuclear infiltrates in the neuropil at all dose levels; however similar findings were not seen in the preceding studies in dogs, including one of 6 month duration. Decreases in lymphocytes and eosinophils in dogs were associated with clinical manifestations of immunosuppression including demodectic mange and bacterial, protozoal and/or yeast infections at all dose levels in the 39-week study. The immunosuppressive effects

generally resolved by end of the recovery phases, with the exception being dogs in which immunosuppression-induced mange became established during treatment. The NOAEL for the 9 month dog study is <0.25 mg/kg/day (1.14 times the maximum recommended human dose (MRHD) on an AUC basis).

In addition to immunosuppression, other potentially treatment-related findings in the 26-week rat study consisted of renal tubular toxicity due to crystal formation, exacerbation of cardiomyopathy with secondary hepatocellular necrosis, and liver inflammation at high doses (100/60 mg/kg/day) of baricitinib. The NOAEL for the 6 month rat study is 5 mg/kg/day (6.8 times the MRHD on an AUC basis).

Carcinogenesis
Baricitinib was not carcinogenic in the 6-month Tg.rasH2 transgenic mouse model at systemic exposures up to156 times (in females) and 111 times (in males) the MRHD. Baricitinib was not carcinogenic in the 2-year carcinogenicity study in rats at systemic exposures up to 54 times (in females) and 12 times (in males) the MRHD.

Mutagenesis
Baricitinib was not mutagenic in the in vitro bacterial mutagenicity assay (Ames assay), or clastogenic in the in vitro chromosome aberration assay, or the in vivo micronucleus assay in rats.

Developmental and Reproductive Toxicity
In a combined male/female rat fertility study, baricitinib was administered to male rats prior to and throughout mating and to female rats prior to mating and up to implantation (Gestation Day 6). Decreased male mating performance (fertility and copulation indices) occurred at baricitinib exposure levels approximately 113 times the MRHD (on an AUC basis at oral doses of 50 mg/kg/day). In female rats, decreased fertility and conception indices, decreased numbers of corpora lutea and implantation sites, increased pre-implantation loss, and/or adverse effects on intrauterine survival of the embryos were observed at baricitinib exposure levels ≥47 times the MRHD (on an AUC basis at oral doses of 25 and 100 mg/kg/day). There was no impairment of female rat fertility at baricitinib exposure levels approximately 8 times the MRHD (on an AUC basis at oral doses of 5 mg/kg/day). Baricitinib exposure levels approximately 24 times the MRHD (on an AUC basis at oral doses of 15 mg/kg/day) had no effect on male fertility, sperm motility, or sperm concentration. Since there were no effects on spermatogenesis (as assessed by histopathology) or semen/sperm endpoints in male rats, the decreased overall mating performance was likely the result of these female effects.

Baricitinib has been shown to reduce fetal growth/weight and produce skeletal malformations in rats and rabbits when given during the period of organogenesis at systemic exposures 16-20 times and 42-84 times, respectively, those in patients at the MRHD.

In a rat embryo fetal developmental study, baricitinib was teratogenic at systemic exposure levels 20 and 110 times the MRHD (on an AUC basis at oral doses of 10 and 40 mg/kg/day, respectively). Teratogenic effects consisted of skeletal malformations [bent limb bone(s) and rib anomaly] and skeletal developmental variations [bent ribs and 7th cervical rib(s)]. In addition,

baricitinib treatment was associated with a reduction in mean fetal weights at exposures110 times the MRHD. No fetal developmental toxicity was observed in rats at exposure levels approximately 4.6 times the MRHD (on an AUC basis at oral doses of 2 mg/kg/day).

In the rabbit embryo fetal developmental study, baricitinib reduced fetal survival and growth (body weight), and resulted in effects on skeletal development (increased mean litter proportions of rib anomaly and vertebral anomaly without associated rib anomaly) were observed at exposures approximately 42 and 84 times the MRHD (on gestation days 7 and 20, respectively, based on AUC at the high oral dose of 30 mg/kg/day). A higher postimplantation loss (both early and late resorptions) with a corresponding decreased litter proportion of viable fetuses was also observed at the same dose/exposures and resulted in a lower gravid uterine weight. These embryofetal findings may have been due, at least in part, to maternal toxicity. No fetal developmental toxicity was observed in rabbits at exposure levels approximately 13 times the MRHD (on an AUC basis at oral doses of 10 mg/kg/day).

In the pre- and post-natal development study in rats, dams were dosed with baricitinib from implantation through lactation at doses up to 25 mg/kg/day. Lower postnatal survival and mean F1 pup body weights and/or body weight gains were observed at the high dose. Decreased pre-weaning pup body weights and body weight gains were observed at 5 mg/kg/day. A higher incidence of malrotated forelimbs in the 25 mg/kg/day group F1 pups (17 pups from 8 litters) compared to the vehicle control group (1 pup affected) that was noted beginning on PND 4 and, with the exception of 5 pups, had ameliorated by PND 21. Mean forelimb and hindlimb grip strength were reduced on PND 20 and 60. No developmental toxicity in the F1 pups was observed at exposure levels less than 4 times the MRHD (on an AUC basis at oral doses of 2 mg/kg/day), and no maternal, F1 behavioral, reproductive, or immunological toxicity was observed at exposure levels 43 times the MRHD (on an AUC basis at doses of 25 mg/kg/day). Plasma baricitinib concentrations in the F1 pups were similar to those in the dams by 8 hours post-dose on postnatal day 4.

REFERENCES

1. Dougados M, van der Heijde D, Chen YC, Greenwald M, Drescher E, Liu J, Beattie S, Witt S, de la Torre I, Gaich C, Rooney T, Schlichting D, de Bono S, Emery P. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. Ann Rheum Dis. 2017 Jan;76(1):88-95.

2. Emery P, Blanco R, Maldonado Cocco J, Chen YC, Gaich CL, DeLozier AM, de Bono S, Liu J, Rooney T, Chang CH, Dougados M. Patient-Reported Outcomes from a Phase 3 Study of Baricitinib in Patients with Conventional Synthetic DMARD-Refractory Rheumatoid Arthritis. RMD Open. 2017.

3. Emery P, McInnes I, Genovese MC, Smolen JS, Kremer J, Dougados M, et al. Characterization of Changes in Lymphocyte Subsets in Baricitinib-treated Patients with Rheumatoid Arthritis in Two Phase 3 Studies. Arthritis Rheumatol. 2015;67(Suppl 10):1364-1365.

4. Fleischmann R, Schiff M, van der Heijde D, Ramos-Remus C, Spindler A, Stanislav M, Zerbini CA, Gurbuz S, Dickson C, de Bono S, Schlichting D, Beattie S, Kuo WL, Rooney T, Macias W, Takeuchi T. Baricitinib, Methotrexate, or Combination in Patients with Rheumatoid Arthritis and No or Limited Prior Disease-Modifying Antirheumatic Drug Treatment. Arthritis Rheumatol. Mar;69(3):506-517.

5. Fridman JS, Scherle PA, Collins R, Burn TC, Li Y, Li J, et al. Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050. J Immunol. 2010;184(9):5298-5307.

6. Genovese MC, Kremer JM, Kartman CE, Schlichting DE, Xie L, Carmack T, Pantojas C, Sanchez Burson J, Tony HP, Macias WL, Rooney TP, Smolen JS. Response to baricitinib based on prior biologic use in patients with refractory rheumatoid arthritis. Rheumatology (Oxford). 2018 May 1;57(5):900-908.

7. Genovese M, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, Beattie S, Koch A, Cardillo T, de Bono S, Rooney T, Macias W, Schlichting D, Smolen J. Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med. 2016;374(13):1243-1252.

8. Keystone EC, Taylor PC, Drescher E, Schlichting DE, Beattie SD, Berclaz PY, Lee CH, Fidelus-Gort RK, Luchi ME, Rooney TP, Macias WL, Genovese MC. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. Ann Rheum Dis. 2015;74(2):333-340.

9. Kremer J, Dougados M , Genovese M, Emery P, Yang L, de Bono S, et al. Response to Baricitinib at 4 Weeks Predicts Response at 12 and 24 Weeks in Patients with

Rheumatoid Arthritis: Results from Two Phase 3 Studies. Arthritis Rheumatol. 2015;67(Suppl 10):1368-1369.

10. Schwartz DM, Bonelli M, Gadina M, O'Shea JJ. Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases. Nat Rev Rheumatol.2016;12(1):25-36

11. Shi JG, Chen X, Lee F, Emm T, Scherle PA, Lo Y, et al. The Pharmacokinetics, Pharmacodynamics, and Safety of Baricitinib, an Oral JAK 1/2 Inhibitor, in Healthy Volunteers. J Clin Pharmacol. 2014;54(12):1354-61.

12. Smolen JS, Kremer JM, Gaich CL, DeLozier AM, Schlichting DE, Xie L, Stoykov I, Rooney T, Bird P, Sánchez Bursón JM, Genovese MC, Combe B. Patient-reported outcomes from a randomised Phase III study of baricitinib in patients with rheumatoid arthritis and an inadequate response to biological agents. Ann Rheum Dis. 2017 Apr;76(4):694-700.

13. Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J, Yakushin S, Ishii T, Emoto K, Beattie S, Arora V, Gaich C, Rooney T, Schlichting D, Macias WL, de Bono S, Tanaka Y. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. N Engl J Med. 2017 Feb 16;376(7):652-662.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION
OLUMIANT™
(Ō-loo'-mē-ant)
baricitinib tablets

Read this carefully before you start taking OLUMIANT and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about OLUMIANT.

Serious Warnings and Precautions

Serious Infections
- You should not take OLUMIANT if you have any kind of infection.
- OLUMIANT is a medicine that affects your immune system and can lower the ability of your body to fight infections, such as tuberculosis, and infections caused by other bacteria, fungi or viruses that can spread throughout the body.
- In some cases, these infections may lead to hospitalization or death.
- Most patients taking OLUMIANT who developed these infections were also taking other medicines, such as methotrexate or corticosteroids that may have made it harder to fight infections.
- If you develop any sign or symptom of an infection (such as fever, sweating, chills, muscle aches, cough, shortness of breath, blood in spit, weight loss, warm, red, or painful skin or sores on your body, diarrhea or stomach pain, burning when you urinate or urinating more often than normal, feeling very tired) contact your healthcare professional.
- Your healthcare professional will closely monitor you for the signs and symptoms of infection during and after the treatment with OLUMIANT.

Cancers
- Lymphoma and other cancers have been reported in patients treated with OLUMIANT.

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.
- If you develop any signs or symptoms of a blood clot in your leg (such as swelling, pain or tenderness in the leg) or in your lung (such as sudden unexplained chest pain or shortness of breath) stop OLUMIANT and seek immediate medical help.

What is OLUMIANT used for?
OLUMIANT, in combination with methotrexate, is indicated for reducing the signs and symptoms of rheumatoid arthritis (RA), in adult patients with moderately to severely active RA who have not responded well to one or more other medicines called disease modifying anti-rheumatic drugs (DMARDs).

OLUMIANT can be used alone if you cannot tolerate methotrexate.

How does OLUMIANT work?
OLUMIANT is believed to interfere with the activity of an enzyme called Janus Kinase (JAK). Normally JAK enzymes help turn on your immune system when you need it. The immune system then causes swelling and tenderness. This is called inflammation. OLUMIANT attaches to JAK enzymes and can help reduce the swelling and tenderness in people with RA.

What are the ingredients in OLUMIANT?
Medicinal ingredient: Baricitinib.

Non-medicinal ingredients: Croscarmellose sodium, ferric oxide, lecithin (soya), magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

OLUMIANT comes in the following dosage form:
Tablets: 2 mg

Do not use OLUMIANT if:
- you are allergic to baricitinib or any of the other ingredients in OLUMIANT.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take OLUMIANT. Talk about any health conditions or problems you may have, including if you:

- have an infection, or if you often get infections. OLUMIANT can make it harder for your body to fight infections. Signs and symptoms of an infection may include:
    - Fever, sweating, or chills
    - Muscle aches
    - Cough
    - Shortness of breath
    - Blood in spit
    - Weight loss
    - Warm, red, or painful skin or sores on your body
    - Diarrhea or stomach pain
    - Burning when you urinate or urinating more often than normal
    - Feeling very tired
- have diabetes, HIV/AIDS, or a weak immune system. People with these conditions have a higher chance of getting infections.
- have or have had tuberculosis (TB), or you have been in close contact with someone with TB.
- have recently traveled to or lived in an area where there is a lot of TB or fungal infections.
- have had a herpes infection, because OLUMIANT may reactivate this condition. Tell your healthcare professional if you develop a painful skin rash with blisters. These can be signs of shingles.
- have, or have previously had, hepatitis B or C.
- have recently received or are scheduled to receive a vaccine. People who take OLUMIANT should not receive live vaccines. Make sure you are up to date with all recommended vaccines before you start treatment with OLUMIANT.
- have or have had any type of cancer.
- have had blood clots in your legs (deep vein thrombosis) or lungs (pulmonary embolism) or have been told you are at risk of blood clots.
- have problems with your blood clotting (thrombophilia).
- plan to become pregnant or are pregnant. If you could become pregnant, you should use effective birth control while you are taking OLUMIANT and for at least 1 week after your last dose. If you become pregnant while taking OLUMIANT contact your healthcare professional immediately.
- plan to breastfeed or are breastfeeding. You and your healthcare provider should decide if you will take OLUMIANT or breastfeed. You should not do both.
- have or have had inflammation in parts of the large intestine (diverticulitis), tears in your stomach or intestines (gastrointestinal perforations) or ulcers in your stomach or intestines. Some people using OLUMIANT get tears in their stomach or intestine. This happens most often in people who also take medicines such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.
- have or have had liver problems.
- have or have had kidney problems.
- have or have had lung problems, including interstitial lung disease.
- have or have had muscle pain or muscle weakness.
- have low blood counts. Treatment with OLUMIANT can be associated with low red blood cell counts (anemia) and low white blood cell counts (neutrophils or lymphocytes).
- have high cholesterol.
- are 65 years of age or older. You may be more likely to get certain side effects.

Other warnings you should know about:

Blood Tests

You will need blood tests before you start OLUMIANT, and while you are taking it, to check if you have a low red blood cell count (anemia), low white blood cell count (neutropenia or lymphopenia), high blood fat (cholesterol) or high levels of liver enzymes, and to ensure that treatment with OLUMIANT is not causing problems. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious Infections

OLUMIANT can make it harder for your body to fight infections. This means that you might get sick more easily which can lead to serious infections. In some cases, these infections may lead to hospitalization or death. Most patients taking OLUMIANT who developed these infections were also taking other medicines, such as methotrexate or corticosteroids that may have made it harder to fight infections. If you have any signs or symptoms of an infection including fever, sweating, or chills, muscle aches, cough, shortness of breath, blood in spit, weight loss, warm, red, or painful skin or sores on your body, diarrhea or stomach pain, burning when you urinate or urinating more often than normal or feeling very tired, while you are being treated with OLUMIANT contact your healthcare professional immediately.

Cancers

OLUMIANT may decrease the activity of your immune system. Medicines that affect the immune system may increase your risk of cancer. Your healthcare professional will monitor you for any signs and symptoms that might mean you have cancer. If you notice any new symptoms while you are being treated with OLUMIANT, including new skin lesions or changes to existing lesions, talk to your healthcare professional.

Blood Clots

Blood clots in the legs and lungs can happen in some people taking OLUMIANT. This may be life-threatening and cause death. If you have any signs or symptoms of blood clots while you are being treated with OLUMIANT, including swelling, pain or tenderness in the leg, sudden unexplained chest pain, or shortness of breath, stop OLUMIANT and seek immediate medical help.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with OLUMIANT:

- probenecid, used to treat gout, since this medicine may increase the levels of OLUMIANT in your blood.
- medicines which are used to control the body's immune response, such as azathioprine, tacrolimus or cyclosporine.
- any other medicines to treat your RA. For example, you should not take rituximab, etanercept, infliximab, anakinra, adalimumab, abatacept, certolizumab, golimumab, tocilizumab, tofacitinib or sarilumab while you are taking OLUMIANT. Using OLUMIANT with these medicines may increase your risk of infection.

How to take OLUMIANT:

- By mouth
- With or without food
- Once a day

Usual adult dose: 2 mg once a day

Overdose:

If you think you have taken too much OLUMIANT, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of OLUMIANT, take your dose as soon as you remember. Do not take more than 1 tablet per day.

What are possible side effects from using OLUMIANT?
These are not all the possible side effects you may feel when taking OLUMIANT. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- upper respiratory tract infections (common cold, sinus infections)
- nose or throat infection with runny or stuffy nose
- cough
- mouth and throat pain
- headaches
- nausea (feeling sick to your stomach)
- vomiting
- diarrhea
- stomach pain
- constipation
- indigestion (heartburn or upset stomach)
- dizziness
- cold sores
- acne
- rash
- high number of platelets (cells involved in blood clotting), shown by blood test
- joint pain, muscle spasms
- back pain
- fatigue
- trouble sleeping

OLUMIANT can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Shingles (herpes zoster): skin rash or blisters usually on one side of the body with itching, burning or tingling pain.			✓
UNCOMMON			
Blood clots in the leg (deep vein thrombosis): swelling, pain or tenderness in the leg			✓
Blood clot in the lung (pulmonary embolism): chest pain, or shortness of breath			✓
Pneumonia (lung infection): coughing, fever, fatigue		✓	
Urinary tract infections: difficulty or increased need to urinate, pain or burning sensation when passing urine, pain in the pelvis or mid-back, urine		✓	

that appears cloudy or bloody			
Cellulitis (skin infection): redness, swelling and painful skin		✓	
Anemia: fatigue, loss of energy, weakness, shortness of breath		✓	
RARE			
Gastroenteritis (infection of the stomach and intestines): vomiting, stomach pain, watery or bloody diarrhea, loss of appetite		✓	
Blood clot in the artery of an arm or leg: cold arm, leg, fingers or hands, muscle pain or spasms, numbness and tingling in the arm or leg			✓
High blood pressure: headache, fatigue, vision problems	✓		
Bronchitis: persistent cough, fatigue, shortness of breath		✓	
Flu: cough, sore throat, feverish chills		✓	
Skin cancer: new skin lesions during or after therapy or if an existing lesion changes in appearance		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or:
- Calling toll-free at 1-866-234-2345

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at room temperature between 15° - 30°C

Keep out of reach and sight of children.

If you want more information about OLUMIANT:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); the manufacturer's website, www.lilly.ca or by calling 1-888-545-5972.

The information in this document is current as of the last revision date shown below. For the most current information please visit our website or contact us directly.

You may need to read this package insert again. Please do not throw it away until you have finished your medicine.

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This leaflet was prepared by Eli Lilly Canada Inc., Toronto, Ontario M1N 2E8.

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