▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PI – OLUMIANT (BARICITINIB)

1 NAME OF THE MEDICINE

OLUMIANT 2mg film-coated tablets
OLUMIANT 4mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

OLUMIANT 2 mg film-coated tablets
Each film-coated tablet contains 2 mg baricitinib

OLUMIANT 4 mg film-coated tablets
Each film-coated tablet contains 4 mg baricitinib

For the full list of excipients, see section 6.1 List of excipients

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

OLUMIANT 2 mg film-coated tablets
Light pink, oblong, debossed with “Lilly” script on one side and “2” on the other.

OLUMIANT 4 mg film-coated tablets
Medium pink, round, debossed with “Lilly” script on one side and “4” on the other.

The tablets contain a recessed area on each face of the tablet surface.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

OLUMIANT is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately, or who are intolerant, to one or more DMARDs.

OLUMIANT can be taken as monotherapy or in combination with cDMARDs, including methotrexate (MTX).

4.2 DOSE AND METHOD OF ADMINISTRATION

Therapy with OLUMIANT should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.

The recommended dose of OLUMIANT is 4 mg once daily. OLUMIANT may be used as monotherapy or in combination with cDMARDS.

A dose of 2 mg once daily may be acceptable for patients with an inadequate response to cDMARDs who have moderate disease severity, limited risk of progressive joint damage and moderate impairment of physical function. (see section 5 PHARMACOLOGICAL PROPERTIES / PHARMACODYNAMIC PROPERTIES / Clinical trials; section 4.4 SPECIAL WARNINGS AND PRECAUTIONS / Use in hepatic impairment, Use in renal impairment, Effects on laboratory tests)

A dose of 2 mg once daily may also be considered for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering.

Combination with other JAK inhibitors has not been studied and is not recommended.

OLUMIANT is given orally with or without food.

Dose Modifications in Patients with Renal Impairment

The recommended dose of OLUMIANT in patients with moderate, Stage 3 renal impairment, (estimated glomerular filtration rate (GFR) 30 - ≤60 mL/min/1.73 m^2) is 2 mg once daily. OLUMIANT is not recommended for use in patients with severe and end stage renal impairment Stage 4 & 5 (estimated GFR of <30 mL/min/1.73 m^2) (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE / Use in renal impairment).

Subjects with creatinine clearance of <40 mL/min at baseline were excluded from participating in the Phase 3 baricitinib studies.

Dose Modifications Due to Drug Interactions

The recommended dose of OLUMIANT in patients taking OAT3 inhibitors with a strong inhibition potential, such as probenecid, is 2 mg once daily (see section 4.5 Interactions with other medicines and other forms of interactions).

Managing Dose Interruptions or Adjustments

Table 1 Laboratory Measures and Monitoring Guidance

Laboratory Measure	Action	Monitoring Guidance
Lipid parameters	Patients should be managed according to local clinical guidelines for hyperlipidaemia	12 weeks after initiation of treatment and thereafter according to local clinical guidelines for hyperlipidaemia
Absolute neutrophil count (ANC)	Treatment should be interrupted if ANC <1x 10^9 cells/L and may be restarted once ANC returns above this value	Before treatment initiation and thereafter according to routine patient management
Absolute lymphocyte count (ALC)	Treatment should be interrupted if ALC <0.5x 10^9 cells/L and may be restarted once ALC returns above this value	
Haemoglobin (Hb)	Treatment should be interrupted if Hb <8 g/dL and may be restarted once Hb returns above this value	
Hepatic transaminases	Treatment should be temporarily interrupted if drug-induced liver injury is suspected	

4.3 CONTRAINDICATIONS

OLUMIANT is contraindicated in patients with known hypersensitivity to baricitinib or any of the excipients in the product.

OLUMIANT must not be used in combination with bDMARDs.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Therapy with OLUMIANT should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.

Identified precautions

Infections

OLUMIANT treatment is associated with an increased rate of infections such as upper respiratory tract infections. OLUMIANT should be used with caution in patients with clinically important chronic, active, or recurrent infection. If an infection develops, monitor carefully and interrupt OLUMIANT therapy if the patient is not responding to standard therapy; do not resume OLUMIANT until the infection resolves.

Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including OLUMIANT (see section 4.8 Adverse effects (Undesirable effects) / Adverse Reactions / Infections.

The most common serious infections reported with OLUMIANT included herpes zoster and cellulitis. Among opportunistic infections, oesophageal candidiasis and pneumocystis pneumonia were reported with OLUMIANT.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with OLUMIANT.

Caution should be used when treating the elderly and patients with diabetes.

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 and the patient should be closely monitored.

If a patient develops a serious infection, administration of OLUMIANT should be interrupted until the infection is controlled.

Tuberculosis

Patients should be screened for tuberculosis (TB) before starting OLUMIANT therapy. OLUMIANT should not be given to patients with active TB. Anti-TB therapy should be considered prior to initiation of OLUMIANT in patients with previously untreated latent TB.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g. herpes zoster including cases that were disseminated beyond the primary or adjacent dermatomes) were reported 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 enrol. Patients with hepatitis B surface antibody and hepatitis B core antibody, without hepatitis B surface antigen, were permitted to enrol; such patients should be monitored for expression of hepatitis B virus (HBV) DNA. Should HBV DNA be detected, consult with a hepatologist.

Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with OLUMIANT.

Venous Thromboembolism

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving OLUMIANT.

For venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), 5 patients (0.5%) treated with baricitinib 4 mg reported events during the 24-week, randomised, placebo-controlled time period of the 6 Phase 2 and Phase 3 RA studies; no events were reported with the 2 mg dose or placebo during this time period. In an analysis of extended data

from the all baricitinib exposure population, 3492 patients (6726 patient-years of observation) with RA, 31 patients experienced a VTE with an exposure-adjusted IR of 0.5 per 100 PY.

OLUMIANT should be used with caution in patients with risk factors for deep vein thrombosis or pulmonary embolism (DVT/PE) such as older age, obesity, a medical history of DVT/PE, or patients undergoing surgery and immobilisation. Patients with multiple risk factors should be closely monitored and consideration should be given to appropriate VTE prophylaxis. If clinical features of DVT/PE occur, interrupt OLUMIANT, evaluate promptly, and institute appropriate treatment. OLUMIANT should only be recommenced once the patient is established on appropriate treatment. Recurrent events of VTE have been reported in some patients recommencing treatment with OLUMIANT.

Malignancy

The risk of malignancy, including lymphoma, is increased in patients with rheumatoid arthritis. Immunomodulatory medicinal products may increase the risk of malignancy.

In the placebo-controlled phase 2/3 clinical studies in rheumatoid arthritis patients, with data up to 24 weeks, 2 malignancies (excluding NMSC) were diagnosed in 2 patients receiving baricitinib 4 mg, compared to 2 malignancies (excluding NMSC) in patients in the placebo group. There were no cases of lymphoma reported during the placebo-controlled studies. In the all baricitinib exposure population of 3464 patients (4214 patient-years of exposure) with RA, 31 patients were diagnosed with malignancies (excluding NMSC), with an exposure-adjusted IR of 0.7 per 100 PY.

Immunisations

No data are available on the response to vaccination with live or inactivated vaccines in patients receiving OLUMIANT. Use with live, attenuated vaccines during, or immediately prior to, OLUMIANT therapy is not recommended. The interval between live vaccinations and initiation of OLUMIANT therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

Use in hepatic impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment. The use of OLUMIANT has not been studied in patients with severe hepatic impairment and is therefore not recommended.

Use in renal impairment

Renal function was found to significantly affect OLUMIANT exposure. The recommended dose of OLUMIANT in patients with moderate, Stage 3 renal impairment, (estimated GFR 30 - ≤60 mL/min/1.73 m^2) is 2 mg once daily. OLUMIANT is not recommended for use in patients with Stage 4 & 5 severe & end stage renal impairment (estimated GFR of <30 mL/min/1.73 m^2). (See Table 1 section 4.2 Dose and method of administration). Patients with a creatinine clearance <40 mL/min were excluded from the Phase 3 studies therefore caution is advised in patients with creatinine clearance 30 - <40 mL/min.

Use in the elderly

Age of ≥65 years or ≥75 years has no effect on OLUMIANT exposure (C_{max} and AUC).

Safety information in patients ≥75 years is limited compared to younger patients and this should be taken into consideration when choosing the dose for these patients.

Paediatric use

The safety and effectiveness of OLUMIANT have not been established in patients under 18 years of age.

Effects on laboratory tests

Neutropenia

Absolute neutrophil counts (ANC) <1000 cells/mm^3 were uncommonly reported in clinical trials. Avoid initiation or interrupt OLUMIANT treatment in patients with an ANC<1000 cells/mm^3 (See Table 1 section 4.2 Dose and method of administration).

Lymphopenia

Absolute lymphocyte counts (ALC) <500 cells/mm^3 were uncommonly reported in clinical trials. Avoid initiation or interrupt OLUMIANT treatment in patients with an ALC <500 cells/mm^3 (See Table 1 section 4.2 Dose and method of administration).

Haemoglobin

Decreases in haemoglobin levels to <8 g/dL were reported uncommonly with baricitinib treatment. Avoid use of OLUMIANT treatment in patients with haemoglobin <8 g/dL (See Table 1 section 4.2 Dose and method of administration).

Lipids

Increases in lipid parameters were very common in the OLUMIANT treated patients in clinical trials. Elevations in low-density lipoprotein (LDL) cholesterol decreased to pre-treatment levels in response to statin therapy. Lipid parameters should be assessed approximately 12 weeks following initiation of OLUMIANT therapy. During 12 weeks of treatment, 33.7% of patients treated with OLUMIANT 4 mg, 20.3 % of patients treated with OLUMIANT 2 mg and 11.3 % of patients treated with placebo developed LDL-C ≥3.36 mmol/L (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) / Adverse Reactions / Lipids). Patients should be managed according to local clinical guidelines for hyperlipidaemia (See Table 1 section 4.2 Dose and method of administration). The effect of these lipid parameter elevations on long-term cardiovascular morbidity and mortality has not been determined.

Aminotransferases

Increases to ≥5 and ≥10x upper limit of normal (ULN) were uncommonly observed for both alanine transaminase (ALT) and aspartate transaminase (AST) in patients treated with OLUMIANT in clinical trials. If increases in ALT or AST are observed, and drug induced liver injury is suspected, OLUMIANT

should be interrupted until this diagnosis is excluded (See Table 1 section 4.2 Dose and method of administration).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Potential for OLUMIANT to affect other drugs

Cytochrome P450 Enzymes

In vitro, baricitinib did not significantly inhibit or induce the activity of cytochrome P450 enzymes (CYPs 3A, 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6). In clinical pharmacology studies, coadministration of baricitinib with the CYP3A substrates simvastatin, ethinyl estradiol, or levonorgestrel resulted in no clinically meaningful changes to these drugs.

Transporters

In vitro, baricitinib did not inhibit the transporters P-glycoprotein (Pgp) or organic anion transporting polypeptide (OATP) 1B1. In vitro, baricitinibdoes inhibit organic anionic transporter (OAT) 1, OAT3, organic cationic transporter (OCT)1, OCT2, OATP1B3, breast cancer resistance protein (BRCP) and multidrug and toxic extrusion protein (MATE)1 and MATE2-K, but clinically meaningful changes to drugs that are substrates for these transporters are unlikely. In clinical pharmacology studies there were no clinically meaningful effects when baricitinib was coadministered with digoxin (Pgp substrate) or methotrexate (substrate of several transporters).

Potential for other drugs to affect OLUMIANT

Cytochrome P450 Enzymes

In vitro, baricitinib is a CYP3A4 substrate. In clinical pharmacology studies, coadministration of baricitinib with ketoconazole (CYP3A inhibitor) resulted in no clinically meaningful effect. Coadministration of baricitinib with fluconazole (CYP3A/CYP2C9 inhibitor) or rifampicin (CYP3A inducer) resulted in no clinically meaningful changes to baricitinib.

Transporters

In vitro, baricitinib is a substrate for OAT3, Pgp, BCRP and MATE2-K. In a clinical pharmacology study, probenecid (OAT3 inhibitor with strong inhibition potential) dosing resulted in approximately a 2-fold increase in $AUC_{(0-\infty)}$ with no change in C_{max} of baricitinib. Simulations with diclofenac and ibuprofen (OAT3 inhibitors with less inhibition potential) predicted no effect on baricitinib exposure. Coadministration of baricitinib with cyclosporine (Pgp/BCRP inhibitor) or methotrexate (substrate of several transporters) resulted in no clinically meaningful effects on baricitinib exposure.

Medicines used for VTE

No clinical drug-drug interaction (DDI) studies with anticoagulants have been conducted. Based on the low DDI potential of baricitinib via enzymes and transporters, clinically meaningful DDI are not anticipated for coadministration of baricitinib with medicines commonly used for prophylaxis or treatment of VTE.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In a combined male/female rat fertility study, baricitinib decreased overall mating performance and male copulation index following dosing at approximately 56x the maximum recommended human exposure (AUC) and induced a dose-related trend towards reduced male fertility index following dosing at approximately 12x the maximum recommended human exposure (AUC).

Baricitinib treatment also significantly decreased female conception index following dosing at approximately 85x human exposure at the maximum recommended dose (AUC) and induced a dose related trend towards decreased fertility index following dosing at approximately 24x the maximum recommended human exposure (AUC). In female rats there were decreased numbers of corpora lutea and implantation sites and increased pre-implantation loss following dosing at approximately 85x human exposure at the maximum recommended dose (AUC). Following dosing at approximately 24x the maximum recommended human exposure (AUC), reduced mean number of viable embryos/dam, reduced mean viable embryos and increased mean post-implantation loss occurred. The no-observed-effects-level (NOEL) for fertility and impaired early embryonic development was approximately 4x human exposure at the maximum recommended dose (AUC).

Since there were no effects on spermatogenesis (as assessed by histopathology) or semen/sperm endpoints in male rats or mating indices in either sex, the decreased overall mating performance was likely the result of effects on female fertility and/or early pre-implantation embryonic development.

Women of childbearing potential should take appropriate precautions to avoid becoming pregnant during treatment with OLUMIANT and for at least 1 week after the final treatment.

Use in pregnancy

Pregnancy Category D

Effects on human foetal development are not known. Based on limited data in rats, baricitinib-associated radioactivity readily crosses the placenta (foetal:maternal ratio approximately 2; n=1). In a rat embryofoetal development study, dosing with baricitinib at maternotoxic doses (approximately ≥10x the human maximum recommended dose; AUC) caused increased incidences of adverse malformations (bent limb bones, rib malformations). An increased incidence of foetal rib variations were also noted at even higher maternal exposures (approximately 55x human exposure at the maximum recommended human dose; AUC). In a rabbit embryofoetal development study, dosing of rabbits at ≤30x human exposure at the maximum recommended dose (AUC comparison) was not associated with foetal malformations or variations. However, maternal dosing at approximately 30x human exposure at the maximum recommended dose (AUC comparison) was associated with a decreased mean number of live foetuses/litter (7% decrease), an increased number of late in utero deaths, and decreased foetal weight.

Although the human relevance of the findings in animal studies is uncertain, the JAK/STAT pathway is involved in cell adhesion and cell polarity, which can affect early embryonic development.

OLUMIANT should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus.

Women of childbearing potential should take appropriate precautions to avoid becoming pregnant during treatment with OLUMIANT and for at least 1 week after the final treatment.

Use in lactation.

It is unknown whether baricitinib is present in human milk. Baricitinib was detected in the milk of lactating rats. Following maternal PO dosing at 2-22x human exposure at the maximum recommended dose (AUC), the maximum plasma levels in pups occurred at 8 hours (last time point measured) post-dose of the dam.

Breastfeeding is not recommended during OLUMIANT treatment.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No specific studies have been conducted to assess driving ability or sedation. There are no known effects on the ability to drive and use machines associated with the use of OLUMIANT.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse Events Reported in Clinical Trials

The safety of OLUMIANT in patients with rheumatoid arthritis (RA) was evaluated in a clinical program consisting of one phase 1 multi-dose study (n=53), three phase 2 multi-dose studies (n=573), four phase 3 multicentre, randomised, double-blind, controlled studies (n=3100), and an ongoing long term extension study.

Tables 2 and 3 list the adverse events (regardless of causality) occurring in ≥1% of patients treated with OLUMIANT during the double-blind, controlled studies.

Table 2 Summary of Adverse Events reported by ≥1% of patients treated with OLUMIANT (all causalities) – double-blind, placebo-controlled studies up to 16 weeks.

	Trials Evaluating OLUMIANT 4 mg (6 Trials) (up to 16 weeks)		Trials Evaluating OLUMIANT 2 mg and OLUMIANT 4 mg (4 Trials) (up to 16 weeks)		
Events	Placebo + cDMARDs n=1070 (%)	OLUMIANT 4 mg + cDMARDs n=997 (%)	Placebo + cDMARDs n=551 (%)	OLUMIANT 2 mg + cDMARDs n=479 (%)	OLUMIANT 4 mg + cDMARDs n=479 (%)
Blood and lymphatic system disorders					
Anaemia	22 (2.1)	20 (2.0)	8 (1.5)	8 (1.7)	6 (1.3)
Gastrointestinal disorders					
Nausea	17 (1.6)	28 (2.8)	11 (2.0)	13 (2.7)	14 (2.9)
Diarrhoea	35 (3.3)	24 (2.4)	21 (3.8)	16 (3.3)	12 (2.5)

Dyspepsia	8 (0.7)	14 (1.4)			
Abdominal pain upper	5 (0.5)	14 (1.4)	3 (0.5)	10 (2.1)	7 (1.5)
Constipation	15 (1.4)	11 (1.1)	9 (1.6)	8 (1.7)	5 (1.0)
Vomiting	6 (0.6)	13 (1.3)	4 (0.7)	11 (2.3)	5 (1.0)
Abdominal pain			4 (0.7)	8 (1.7)	3 (0.6)
General disorders and administration site conditions					
Fatigue	14 (1.3)	11 (1.1)	8 (1.5)	7 (1.5)	8 (1.7)
Pyrexia			3 (0.5)	6 (1.3)	6 (1.3)
Oedema peripheral			8 (1.5)	5 (1.0)	2 (0.4)
Hepatobiliary disorders					
Hepatic function abnormal			1 (0.2)	5 (1.0)	2 (0.4)
Infections and infestations					
Nasopharyngitis	51 (4.8)	53 (5.3)	26 (4.7)	16 (3.3)	25 (5.2)
Upper respiratory tract infection	39 (3.6)	46 (4.6)	25 (4.5)	27 (5.6)	31 (6.5)
Bronchitis	30 (2.8)	31 (3.1)	19 (3.4)	12 (2.5)	14 (2.9)
Urinary tract infection	29 (2.7)	34 (3.4)	14 (2.5)	17 (3.5)	16 (3.3)
Pharyngitis	14 (1.3)	23 (2.3)	4 (0.7)	10 (2.1)	13 (2.7)
Gastroenteritis	9 (0.8)	16 (1.6)	4 (0.7)	7 (1.5)	12 (2.5)
Influenza	10 (0.9)	18 (1.8)	6 (1.1)	6 (1.3)	9 (1.9)
Herpes zoster	4 (0.4)	14 (1.4)	2 (0.4)	5 (1.0)	9 (1.9)
Sinusitis	12 (1.1)	10 (1.0)	6 (1.1)	10 (2.1)	6 (1.3)
Oral herpes	4 (0.4)	10 (1.0)			
Rhinitis			1 (0.2)	6 (1.3)	1 (0.2)
Cystitis			5 (0.9)	7 (1.5)	1 (0.2)
Injury, poisoning and procedural complications					
Contusion			7 (1.3)	6 (1.3)	2 (0.4)
Investigations					
Blood creatine phosphokinase increased	6 (0.6)	35 (3.5)	3 (0.5)	11 (2.3)	24 (5.0)
Alanine aminotransferase increased	10 (0.9)	15 (1.5)	6 (1.1)	5 (1.0)	8 (1.7)
Aspartate aminotransferase increased	5 (0.5)	14 (1.4)	4 (0.7)	2 (0.4)	10 (2.1)
Metabolism and nutrition disorders					
Hypercholesterolaemia	14 (1.3)	28 (2.8)	7 (1.3)	7 (1.5)	16 (3.3)
Hyperlipidaemia	8 (0.7)	19 (1.9)	6 (1.1)	5 (1.0)	9 (1.9)
Dyslipidaemia	5 (0.5)	10 (1.0)	2 (0.4)	6 (1.3)	5 (1.0)
Musculoskeletal and connective tissue disorders					
Arthralgia	17 (1.6)	17 (1.7)	10 (1.8)	8 (1.7)	11 (2.3)
Rheumatoid arthritis	23 (2.1)	14 (1.4)	10 (1.8)	5 (1.0)	10 (2.1)
Back pain	26 (2.4)	12 (1.2)	18 (3.3)	14 (2.9)	7 (1.5)
Muscle spasms			3 (0.5)	6 (1.3)	5 (1.0)
Myalgia			1 (0.2)	4 (0.8)	5 (1.0)
Nervous system disorders					
Headache	32 (3.0)	38 (3.8)	22 (4.0)	30 (6.3)	20 (4.2)
Dizziness	8 (0.7)	14 (1.4)	4 (0.7)	7 (1.5)	7 (1.5)
Psychiatric disorders					

Insomnia			3 (0.5)	5 (1.0)	2 (0.4)
Reproductive system and breast disorders					
Erectile dysfunction (a)			0	0	1 (1.1)
Respiratory, thoracic and mediastinal disorders					
Cough	17 (1.6)	19 (1.9)	9 (1.6)	9 (1.9)	13 (2.7)
Oropharyngeal pain	5 (0.5)	12 (1.2)	3 (0.5)	9 (1.9)	11 (2.3)
Skin and subcutaneous tissue disorders					
Alopecia			5 (0.9)	0	9 (1.9)
Acne			0	1 (0.2)	5 (1.0)
Rash			3 (0.5)	7 (1.5)	5 (1.0)
Vascular disorders					
Hypertension	17 (1.6)	21 (2.1)	6 (1.1)	16 (3.3)	15 (3.1)

(a) denominator adjusted because event is specific to males: N=93 (placebo), N=93 (OLUMIANT 2 mg), N=88 (OLUMIANT 4 mg)

Table 3 Summary of Adverse Events reported by ≥1% of patients treated with OLUMIANT (all causalities) – double-blind, active-controlled study up to 24 weeks (RA-BEGIN).

	Trial Evaluating OLUMIANT 4 mg (1 Trial) (up to 24 weeks)		
Events	**Methotrexate n=210 (%)**	**OLUMIANT 4 mg n=159 (%)**	**OLUMIANT 4 mg + methotrexate n=215 (%)**
Blood and lymphatic system disorders			
Anaemia	2 (1.0)	2 (1.3)	4 (1.9)
Iron deficiency anaemia	0	1 (0.6)	3 (1.4)
Thrombocytosis	0	3 (1.9)	2 (0.9)
Cardiac disorders			
Coronary artery disease	0	2 (1.3)	0
Eye disorders			
Vision blurred	0	0	3 (1.4)
Cataract	1 (0.5)	2 (1.3)	1 (0.5)
Gastrointestinal disorders			
Nausea	11 (5.2)	7 (4.4)	16 (7.4)
Dyspepsia	0	2 (1.3)	8 (3.7)
Constipation	2 (1.0)	1 (0.6)	5 (2.3)
Stomatitis	1 (0.5)	1 (0.6)	4 (1.9)
Abdominal discomfort	1 (0.5)	1 (0.6)	3 (1.4)
Diarrhoea	9 (4.3)	3 (1.9)	3 (1.4)
Gastrooesophageal reflux disease	1 (0.5)	0	3 (1.4)
Abdominal pain upper	4 (1.9)	3 (1.9)	1 (0.5)
Vomiting	4 (1.9)	4 (2.5)	1 (0.5)
General disorders and administration site conditions			
Pyrexia	4 (1.9)	1 (0.6)	6 (2.8)

Fatigue	4 (1.9)	4 (2.5)	5 (2.3)
Drug intolerance	2 (1.0)	2 (1.3)	0
Oedema peripheral	1 (0.5)	3 (1.9)	0
Hepatobiliary disorders			
Hepatic function abnormal	4 (1.9)	1 (0.6)	6 (2.8)
Infections and infestations			
Nasopharyngitis	11 (5.2)	11 (6.9)	14 (6.5)
Upper respiratory tract infection	13 (6.2)	7 (4.4)	10 (4.7)
Urinary tract infection	2 (1.0)	4 (2.5)	10 (4.7)
Pharyngitis	3 (1.4)	2 (1.3)	5 (2.3)
Sinusitis	2 (1.0)	1 (0.6)	5 (2.3)
Gastroenteritis	2 (1.0)	3 (1.9)	4 (1.9)
Influenza	1 (0.5)	4 (2.5)	4 (1.9)
Vulvovaginal candidiasis (b)	1 (0.7)	0	4 (2.6)
Bronchitis	3 (1.4)	2 (1.3)	3 (1.4)
Cystitis	0	1 (0.6)	3 (1.4)
Herpes zoster	1 (0.5)	3 (1.9)	3 (1.4)
Tonsillitis	1 (0.5)	2 (1.3)	1 (0.5)
Onychomycosis	1 (0.5)	2 (1.3)	0
Investigations			
Blood creatine phosphokinase increased	0	4 (2.5)	9 (4.2)
Alanine aminotransferase increased	2 (1.0)	1 (0.6)	9 (4.2)
Aspartate aminotransferase increased	1 (0.5)	0	4 (1.9)
Blood alkaline phosphatase increased	1 (0.5)	1 (0.6)	4 (1.9)
Low density lipoprotein increased	1 (0.5)	1 (0.6)	3 (1.4)
Liver function test abnormal	1 (0.5)	2 (1.3)	2 (0.9)
Blood cholesterol increased	0	2 (1.3)	1 (0.5)
Platelet count increased	0	2 (1.3)	1 (0.5)
Weight increased	2 (1.0)	3 (1.9)	1 (0.5)
White blood cell count increased	0	2 (1.3)	0
Metabolism and nutrition disorders			
Dyslipidaemia	2 (1.0)	2 (1.3)	6 (2.8)
Hyperlipidaemia	0	3 (1.9)	5 (2.3)
Hypercholesterolaemia	3 (1.4)	4 (2.5)	4 (1.9)
Musculoskeletal and connective tissue disorders			
Back pain	3 (1.4)	2 (1.3)	5 (2.3)
Muscle spasms	1 (0.5)	2 (1.3)	6 (2.8)
Osteoarthritis	0	2 (1.3)	1 (0.5)
Nervous system disorders			
Headache	1 (0.5)	4 (2.5)	5 (2.3)

Dizziness	4 (1.9)	0	3 (1.4)
Sciatica	0	3 (1.9)	0
Depression	3 (1.4)	6 (3.8)	1 (0.5)
Reproductive system and breast disorders			
Benign prostatic hyperplasia (a)	0	0	1 (1.7)
Respiratory, thoracic and mediastinal disorders			
Cough	11 (5.2)	4 (2.5)	4 (1.9)
Oropharyngeal pain	1 (0.5)	2 (1.3)	2 (0.9)
Dyspnea	4 (1.9)	2 (1.3)	0
Rhinorrhea	0	2 (1.3)	0
Skin and subcutaneous tissue disorders			
Alopecia	4 (1.9)	1 (0.6)	5 (2.3)
Acne	0	2 (1.3)	2 (0.9)
Dermatitis contact	2 (1.0)	2 (1.3)	2 (0.9)
Vascular disorders			
Hypertension	5 (2.4)	1 (0.6)	9 (4.2)

(a) denominator adjusted because event is specific to males: N=62 (MTX), N=38 (OLUMIANT 4 mg), N=59 (OLUMIANT 4 mg + MTX)
(b) denominator adjusted because event is specific to females: N=148 (MTX), N=121 (OLUMIANT4 mg), N=156 (OLUMIANT 4 mg + MTX)

Venous thromboembolism

Events of VTE, including DVT and PE, have been reported in clinical trials (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE / Identified precautions / Venous Thromboembolism)

Treatment-Naïve Patients

RA-BEGIN evaluated 584 patients with moderate to severe RA who had no or limited exposure to MTX and who were naïve to other DMARDs. The safety profile observed in the OLUMIANT treatment groups was consistent with the overall safety profile of OLUMIANT across all treatment settings. Up to week 52, similar proportions of patients in each of the 3 treatment groups experienced a treatment-emergent adverse event: MTX alone 71.9%, OLUMIANT 4 mg monotherapy 71.1%, and OLUMIANT 4 mg + MTX 77.7%. Likewise, similar proportions of patients experienced serious adverse events (SAEs): MTX alone 9.5%, OLUMIANT 4 mg monotherapy 7.5%, and OLUMIANT 4 mg + MTX 7.9%. Adverse events leading to discontinuation of study drug were most frequent in patients taking baricitinib in combination with MTX: MTX alone 5.2%, OLUMIANT 4 mg monotherapy 5.7%, and OLUMIANT 4 mg +MTX 10.7%. The most common reason for treatment discontinuation was infections or infestations. Three patient deaths were reported during the study, all in the MTX alone group.

Methotrexate Inadequate Responders

RA-BEAM evaluated 1305 patients with moderate to severe RA who had had an inadequate response to methotrexate and had not been treated with biologic DMARDs. Patients in this study were randomised to receive placebo, baricitinib or adalimumab. The safety profile observed in the baricitinib treatment groups was consistent with the overall safety profile of baricitinib across all treatment settings. Up to week 24, a higher proportion of patients in the 2 active treatment groups

experienced a treatment-emergent adverse event: placebo 60.5%, baricitinib 4 mg 71.3%, and adalimumab 67.9%. Higher proportions of patients experienced serious adverse events (SAEs) in the placebo (4.5%) and baricitinib 4 mg (4.7%) treatment groups compared to adalimumab (1.8%). Adverse events leading to discontinuation of study drug were most frequent in patients taking baricitinib 4 mg (5.1%) compared to placebo (3.5%) and adalimumab (2.1%). The most common reason for treatment discontinuation was infections or infestations.

Adverse Reactions

Adverse Drug Reactions (ADRs) from rheumatoid arthritis clinical studies are presented below by System Organ Class (SOC) and frequency categories, defined using the following convention: very common (≥10%); common (≥1% to <10%), uncommon (≥0.1% to <1%) or rare (≥0.01% to <0.1%).

Common Clinical Trial Adverse Drug Reactions (≥1%).

Gastrointestinal disorders
Common: nausea

Infections and infestations
Very common: upper respiratory tract infections
Common: herpes simplex; herpes zoster

Laboratory parameters

Clinical chemistry
Very common: LDL cholesterol ≥130 mg/dL (≥3.36 mmol/L)
Common: ALT≥3x ULN

Haematology
Common: thrombocytosis >600,000 cells/mm^3

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Skin and subcutaneous tissue disorders
Uncommon: acne

Laboratory parameters

Clinical chemistry
Uncommon: Creatine phosphokinase >5x ULN; Triglycerides ≥500 mg/dL (≥5.65 mmol/L); AST ≥3x ULN

Haematology
Uncommon: neutropenia <1000 cells/mm^3

Description of selected adverse reactions

Infections

Events related to upper respiratory tract infections, herpes simplex, and herpes zoster were commonly observed during controlled clinical trials. Most infections (as observed in 95% of patients reporting an infection) were mild to moderate in severity.

Serious infections occurred in 1.0% of patients treated with OLUMIANT 4 mg (6 study dataset), 1.3% with OLUMIANT 2 mg (4 study dataset) and 1.0% of patients treated with placebo (6 study dataset) during the initial 12 week period. In RA-BEGIN, the serious infection rate during the 24 week treatment period was 1.3% with OLUMIANT 4 mg monotherapy, 1.9% with OLUMIANT 4 mg plus methotrexate, and 1.4% with methotrexate monotherapy. The most common serious infections were herpes zoster and cellulitis.

Nausea

In treatment-naïve patients, through 52 weeks, the frequency of nausea was greater for the combination treatment of methotrexate and OLUMIANT (9.3%) compared to methotrexate alone (6.2%) or OLUMIANT alone (4.4%). Nausea was most frequent during the first 2 weeks of treatment.

Laboratory Parameters

Neutropenia

In controlled clinical trials, neutrophil counts below 1000 cells/mm^3 occurred in 0.3% of patients treated with OLUMIANT 4 mg, 0.6% of patients treated with OLUMIANT 2 mg, and 0% of patients treated with placebo during the initial 12 week treatment period. In RA-BEGIN, decreases in neutrophil counts below 1000 cells/mm^3 during the 24 week treatment period did not occur in any patient treated with OLUMIANT 4 mg monotherapy, with OLUMIANT 4 mg plus methotrexate, or with methotrexate monotherapy. In the all-exposure population, the pattern and incidence of decreases in neutrophil counts remained consistent with observations in the controlled periods of the studies.

No association was observed between decreases in neutrophil counts and the occurrence of serious infections. In clinical studies, treatment was interrupted in response to absolute neutrophil counts <1000 cells/mm^3 (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE / Identified precautions).

Thrombocytosis

In controlled clinical trials, increases in platelet counts above 600,000 cells/mm^3 occurred in 1.7% of patients treated with OLUMIANT 4 mg, 1.1% of patients treated with OLUMIANT 2 mg, and 0.9% of patients treated with placebo during the 12 week treatment period. In RA-BEGIN, increases in platelet counts above 600,000 cells/mm^3 during the 24 week treatment period occurred in 2.6% of patients treated with OLUMIANT 4 mg monotherapy, 1.9% of patients treated with OLUMIANT 4 mg plus methotrexate, and 2.4% of patients treated with methotrexate monotherapy.

In the all exposure population, the pattern and incidence of increases in platelet counts remained consistent with observations in the controlled periods of the studies.

Liver Enzyme Elevations

Events of increases in liver enzymes ≥3x ULN were observed in patients treated with OLUMIANT.

ALT elevations ≥3x ULN during the 12 week treatment period occurred in 1.3% of patients treated with OLUMIANT 4 mg, 1.5% with OLUMIANT 2 mg, and 1.0% with placebo.

AST elevations ≥3x ULN during the 12 week treatment period occurred in 0.7% of patients treated with OLUMIANT 4 mg, 1.0% with OLUMIANT 2 mg, and 0.8% of patients receiving placebo.

In RA-BEGIN, ALT and AST elevations ≥3x ULN during the 24 week treatment period occurred in 1.9% and 1.3% of patients treated with OLUMIANT 4 mg monotherapy, 4.7% and 1.9% of patients treated with OLUMIANT 4 mg plus methotrexate, and 1.9% and 0% of patients treated with methotrexate monotherapy (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE / Identified precautions).

Lipids

In controlled clinical trials, OLUMIANT treatment was associated with increases in lipid parameters including total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol. Elevations were observed at 12 weeks and remained stable thereafter. During 12 weeks of treatment, 33.7% of patients treated with OLUMIANT 4 mg, 20.3 % of patients treated with OLUMIANT 2 mg and 11.3 % of patients treated with placebo developed LDL-C ≥3.36 mmol/L.

Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy.

While increases were observed in LDL and triglycerides, the mean LDL/HDL ratio remained stable. In the all-exposure population, the pattern and incidence of increases in LDL and triglycerides remained consistent with observations in the controlled periods of the studies (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE / Identified precautions).

Creatine Phosphokinase (CPK)

In controlled clinical trials, OLUMIANT treatment was associated with CPK elevations >5x ULN in 0.7% of patients treated with OLUMIANT 4 mg, 0.2% of patients treated with OLUMIANT 2 mg, and 0.3% of patients treated with placebo during the 12 week treatment period. In RA-BEGIN, CPK elevations >5x ULN during the 24 week treatment period occurred in 0.6% of patients treated with OLUMIANT 4 mg monotherapy, 4.3% of patients treated with OLUMIANT 4 mg plus methotrexate, and 0% of patients treated with methotrexate monotherapy.

In the all exposure population, there were no confirmed cases of rhabdomyolysis. The pattern and incidence of increases in CPK remained consistent with observations in the controlled periods of the studies.

4.9 OVERDOSE

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-liming 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 be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 haematopoiesis, inflammation and immune function. Within the intracellular signalling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs), which activate gene expression within the cell. OLUMIANT contains baricitinib which modulates these signalling pathways by partially inhibiting JAK1 and JAK2 enzymatic activity, thereby reducing the phosphorylation and activation of STATs.

Baricitinib is a selective and reversible inhibitor of JAK1 and JAK2. 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.

Pharmacodynamics

OLUMIANT inhibition of IL-6 induced STAT3 phosphorylation

OLUMIANT administration resulted in a dose dependent inhibition of IL-6 induced STAT3 phosphorylation in whole blood from healthy subjects with maximal inhibition observed 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 (RA), decreases in serum C-reactive protein (CRP) were observed as early as 1 week after starting treatment with OLUMIANT and were maintained throughout dosing.

Clinical trials

The efficacy and safety of OLUMIANT was assessed in four randomised, double-blind, multicentre studies in patients with active RA (Table 4). The patients were diagnosed according to American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 criteria. Patients over 18 years of age were eligible if at least 6 tender and 6 swollen joints were present at baseline. All patients who completed these studies were eligible to enrol in a long term extension study for up to 4 years continued treatment.

Table 4 Summary of Clinical Trials

Study name (duration)	**Population** (Number randomised)	**Treatment arms**	**Summary of key outcome measures**
RA-BEGIN (52 weeks)	MTX-naive[1] (584)	· OLUMIANT 4 mg QD · OLUMIANT 4 mg QD + MTX · MTX	Primary endpoints: · ACR20 at week 24 Other endpoints: · Physical function (HAQ-DI) · Radiographic progression (mTSS) · Low disease activity and remission (SDAI, DAS28-hsCRP)
RA-BEAM (52 weeks)	MTX-IR[2] (1305)	· OLUMIANT 4 mg QD · Adalimumab 40 mg SC Q2W · Placebo All patients on background MTX	Primary endpoints: · ACR20 at week 12 Other endpoints: · Physical function (HAQ-DI) · Radiographic progression (mTSS) · Low disease activity and remission (SDAI, DAS28-hsCRP) · Morning joint stiffness (duration and severity) · Worst tiredness · Worst joint pain · Radiographic progression (mTSS) · ACR50 · ACR70
RA-BUILD (24 weeks)	cDMARD-IR[3] (684)	· OLUMIANT 4 mg QD · OLUMIANT 2 mg QD · Placebo On background cDMARDs if on stable cDMARD at study entry	Primary endpoints: · ACR20 at week 12 Other endpoints: · Physical function (HAQ-DI) · Radiographic progression (mTSS) · Low disease activity and remission (SDAI,DAS28-hsCRP) · Morning joint stiffness (duration and severity) · Worst tiredness · Worst joint pain
RA-BEACON (24 weeks)	TNF-IR[4] (527)	· OLUMIANT 4 mg QD · OLUMIANT 2 mg QD · Placebo On background cDMARDs	Primary endpoints: · ACR20 at week 12 Other endpoints: · Physical function (HAQ-DI) · Low disease activity and remission (SDAI,DAS28-hsCRP)
RA-BEYOND	Long Term Extension (2539)	· OLUMIANT 4 mg QD · OLUMIANT 2 mg QD	Primary endpoints: · Safety and tolerability assessments Other Endpoints · Durability of ACR20/50/70 response · Durability of low disease activity or remission (DAS28-hsCRP, DAS28-ESR, SDAI, and CDAI)

Abbreviations: QD = Once daily; Q2W = Once every 2 weeks; SC = Subcutaneously;
[1] Patients who had received less than 3 doses of Methotrexate (MTX); naïve to other conventional or biologic DMARDs
[2] Patients who had an inadequate response to MTX (+/- other cDMARDs); biologic-naive
[3] Patients who had an inadequate response or were intolerant to ≥1 cDMARDs; biologic-naive
[4] Patients who had an inadequate response or were intolerant to ≥1 bDMARDs; including at least one TNF inhibitor

Clinical Response

In all studies, patients treated with OLUMIANT 4 mg once daily had statistically significantly higher ACR20/50 responses at 12 weeks compared to placebo, methotrexate (MTX) and adalimumab. ACR70 responses in patients treated with OLUMIANT 4 mg once daily were statistically significantly higher at 12 weeks compared to placebo and MTX (see Table 5 and Table 6). Time to onset of efficacy was rapid across measures with greater responses seen as early as week 1. Continued, durable response rates were observed, with ACR20/50/70 responses maintained for at least 2 years including the long-term extension study.

Treatment with OLUMIANT 4 mg, alone or in combination with cDMARDs, resulted in significant improvements in all individual ACR components, including tender and swollen joint counts, patient and physician global assessments, HAQ-DI, pain assessment, and CRP, compared to placebo or MTX monotherapy.

In RA-BEAM, treatment with OLUMIANT 4 mg resulted in improvements in patient and physician global assessments, HAQ-DI, pain assessment and CRP at weeks 12, 24, and 52 compared to adalimumab. The percentage of patients who achieved ACR20 response by visit within this study is shown in Figure 1.

In placebo-controlled trials in which MTX was not required, 501 subjects randomised to OLUMIANT 2 mg or 4 mg received MTX as background therapy, and 303 received cDMARDs other than MTX (approximately half with MTX and half without). The most common concomitant disease-modifying antirheumatic drugs (DMARDs) in these subjects were MTX (79% of patients), hydroxychloroquine (19%), leflunomide (11%), and sulphasalazine (9%). No relevant differences regarding efficacy and safety were observed in subgroups defined by types of concomitant DMARDs used in combination with OLUMIANT.

Remission and Low Disease Activity

A statistically significantly greater proportion of patients treated with OLUMIANT 4 mg compared to placebo or MTX achieved remission, as defined by Simplified Disease Activity Index (SDAI) ≤3.3, at weeks 12 and 24 (see Tables 7 and 8). Similarly, when defined by Clinical Disease Activity Index (CDAI) ≤2.8, a greater proportion of patients treated with OLUMIANT 4 mg compared to placebo or MTX achieved remission at weeks 12 and 24.

In all 4 completed studies, a higher proportion of patients treated with OLUMIANT 4 mg compared to placebo or MTX achieved low disease activity or remission (Disease Activity Score 28-erythrocyte sedimentation rate [DAS28-ESR] or Disease Activity Score 28-high sensitivity C-reactive protein [DAS28-hsCRP] ≤3.2 and DAS28-ESR or DAS28-hsCRP <2.6) at weeks 12 and 24.

Greater rates of remission compared to placebo were observed as early as week 4. Including data from a long-term extension study, remission and low disease activity rates were maintained for at least 2 years.

Table 5 ACR Response Rates – Active Comparator Trials

	Percent of Patients					
	DMARD-naïve			MTX-IR		
	Study RA-BEGIN			Study RA-BEAM		
	MTX	OLUMIANT 4 mg/day	OLUMIANT 4 mg/day + MTX	Placebo + MTX	OLUMIANT 4 mg/day + MTX	Adalimumab 40 mg Every Other Week + MTX
N	**210**	**159**	**215**	**488**	**487**	**330**
ACR 20						
Week 12	59 %	79 %***	77 %***	40 %	70 %***†	61 %***
Week 24	62 %	77 %**	78 %***	37 %	74 %***†	66 %***
Week 52	56 %	73 %***	73 %***		71 %††	62 %
ACR 50						
Week 12	33 %	55 %***	60 %***	17 %	45 %***††	35 %***
Week 24	43 %	60 %**	63 %***	19 %	51 %***	45 %***
Week 52	38 %	57 %***	62 %***		56 %†	47 %
ACR 70						
Week 12	16 %	31 %***	33 %***	5 %	19 %***†	13 %***
Week 24	21 %	42 %***	40 %***	8 %	30 %***†	22 %***
Week 52	25 %	42 %***	46 %***		37 %	31 %

Abbreviations: MTX = methotrexate
** p ≤ 0.01; *** p ≤ 0.001 vs. placebo (vs. MTX for RA-BEGIN)
† p ≤ 0.05; †† p ≤ 0.01;

Table 6 ACR Response Rates – Placebo Controlled Trials

	Percent of Patients					
	cDMARD-IR			TNFi-IR		
	Study RA-BUILD			Study RA-BEACON		
	Placebo + cDMARDs	OLUMIANT 2 mg/day + cDMARDs	OLUMIANT 4 mg/day + cDMARDs	Placebo + cDMARDs	OLUMIANT 2 mg/day + cDMARDs	OLUMIANT 4 mg/day + cDMARDs
N	**228**	**229**	**227**	**176**	**174**	**177**
ACR 20						
Week 12	39 %	66 %***	62 %***	27 %	49 %***	55 %***
Week 24	42 %	61 %***	65 %***	27 %	45 %***	46 %***
ACR 50						
Week 12	13 %	34 %***	33 %***	8 %	20 %**	28 %***
Week 24	21 %	41 %***	44 %***	13 %	23 %*	29 %***
ACR 70						
Week 12	3 %	18 %***	18 %***	2 %	13 %***	11 %**
Week 24	8 %	25 %***	24 %***	3 %	13 %***	17 %***

* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001 vs. placebo

Table 7 Low Disease Activity and Clinical Remission – Active Comparator Trials

	Percent of Patients					
	DMARD-naïve			MTX-IR		
	Study RA-BEGIN			Study RA-BEAM		
	MTX	OLUMIANT 4 mg/day	OLUMIANT 4 mg/day + MTX	Placebo + MTX	OLUMIANT 4 mg/day + MTX	Adalimumab 40 mg Every Other Week + MTX
N	**210**	**159**	**215**	**488**	**487**	**330**
SDAI ≤3.3[a]						
Week 12	6 %	14 %*	20 %***	2 %	8 %***	7 %***
Week 24	10 %	22 %**	23 %**	3 %	16 %***	14 %***
Week 52	13 %	25 %**	30 %***		23 %	18 %
CDAI ≤2.8[b]						
Week 12	7 %	14 %*	19 %***	2 %	8 %***	7 %**
Week 24	11 %	21 %**	22 %**	4 %	16 %***	12 %***
Week 52	16 %	25 %*	28 %**		22 %	18 %
DAS28-hsCRP ≤3.2[c]						
Week 12	30 %	47 %***	56 %***	14 %	44 %***††	35 %***
Week 24	38 %	57 %***	60 %***	19 %	52 %***	48 %***
Week 52	38 %	57 %***	63 %***		56 %†	48 %
DAS28-ESR ≤3.2[d]						
Week 12	15 %	21 %	34 %***	7 %	24 %***	21 %***
Week 24	23 %	36 %**	39 %***	10 %	32 %***	34 %***
Week 52	27 %	36 %	45 %***		39 %	36 %
HAQ-DI Minimum Clinically Important Difference (decrease in score of ≥0.30):[e]						
Week 12	60 %	81 %***	77 %***	46 %	68 %***	64 %***
Week 24	66 %	77 %*	74 %	37 %	67 %***†	60 %***
Week 52	53 %	65 %*	67 %**		61 %	55 %

* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001 vs. placebo (vs. MTX for RA-BEGIN)
† p ≤ 0.05; †† p ≤ 0.01; vs. adalimumab
[a] Simplified Disease Activity Index
[b] Clinical Disease Activity Index
[c] Disease Activity Score 28-high sensitivity C-reactive protein
[d] Disease Activity Score 28-erythrocyte sedimentation rate
[e] Health Assessment Questionnaire–Disability Index

Table 8 Low Disease Activity and Clinical Remission – Placebo Controlled Trials

	Percent of Patients					
	cDMARD-IR			TNFi-IR		
	Study RA-BUILD			Study RA-BEACON		
	Placebo + cDMARDs	OLUMIANT 2 mg/day + cDMARDs	OLUMIANT 4 mg/day + cDMARDs	Placebo + cDMARDs	OLUMIANT 2 mg/day + cDMARDs	OLUMIANT 4 mg/day + cDMARDs
N	**228**	**229**	**227**	**176**	**174**	**177**
SDAI ≤3.3[a]						
Week 12	1 %	9 %***	9 %***	2 %	2 %	5 %
Week 24	4 %	17 %***	15 %***	2 %	5 %	9 %**
CDAI ≤2.8[b]						
Week 12	2 %	10 %***	9 %***	2 %	3 %	6 %
Week 24	4 %	15 %***	15 %***	3 %	5 %	9 %*
DAS28-hsCRP ≤3.2[c]						
Week 12	17 %	36 %***	39 %***	9 %	24 %***	32 %***
Week 24	24 %	46 %***	52 %***	11 %	20 %*	33 %***
DAS28-ESR ≤3.2[d]						
Week 12	7 %	21 %***	22 %***	4 %	13 %**	12 %**
Week 24	10 %	29 %***	32 %***	7 %	11 %	17 %**
HAQ-DI Minimum Clinically Important Difference (decrease in score of ≥0.30):[e]						
Week 12	44 %	60 %***	56 %**	35 %	48 %*	54 %***
Week 24	37 %	58 %***	55 %***	24 %	41 %***	44 %***

* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001 vs. placebo

[a] Simplified Disease Activity Index

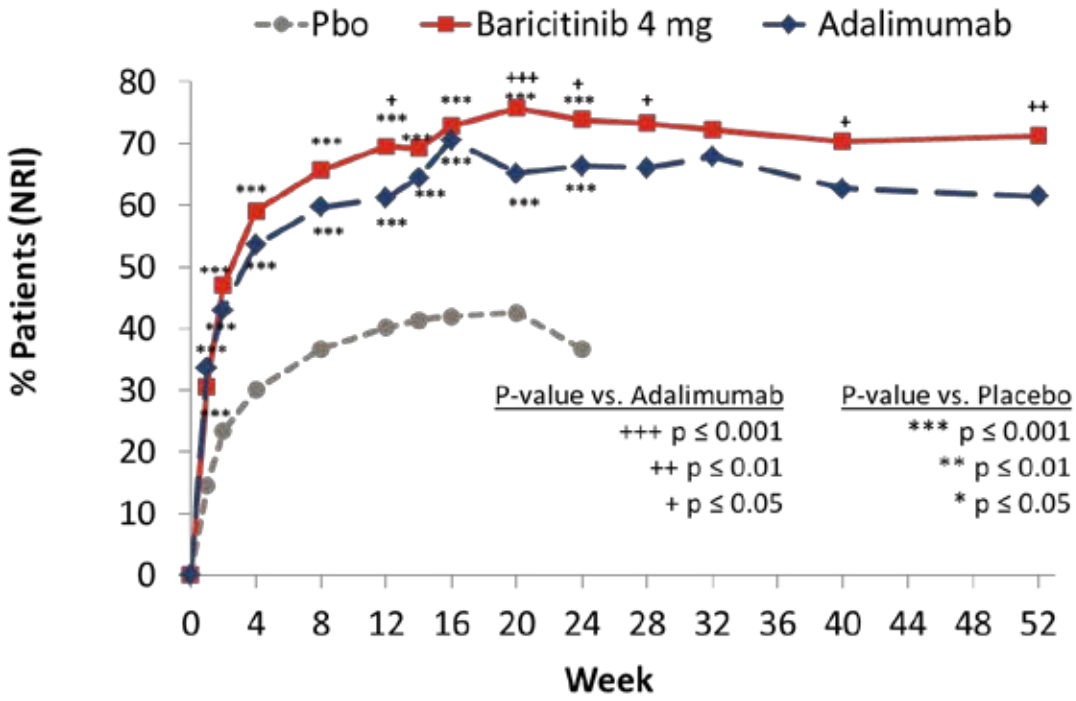
[b] Clinical Disease Activity Index

[c] Disease Activity Score 28-high sensitivity C-reactive protein

[d] Disease Activity Score 28-erythrocyte sedimentation rate

[e] Health Assessment Questionnaire–Disability Index

Figure 1 Percent of Patients Achieving ACR20 in RA-BEAM (mITT, using NRI)

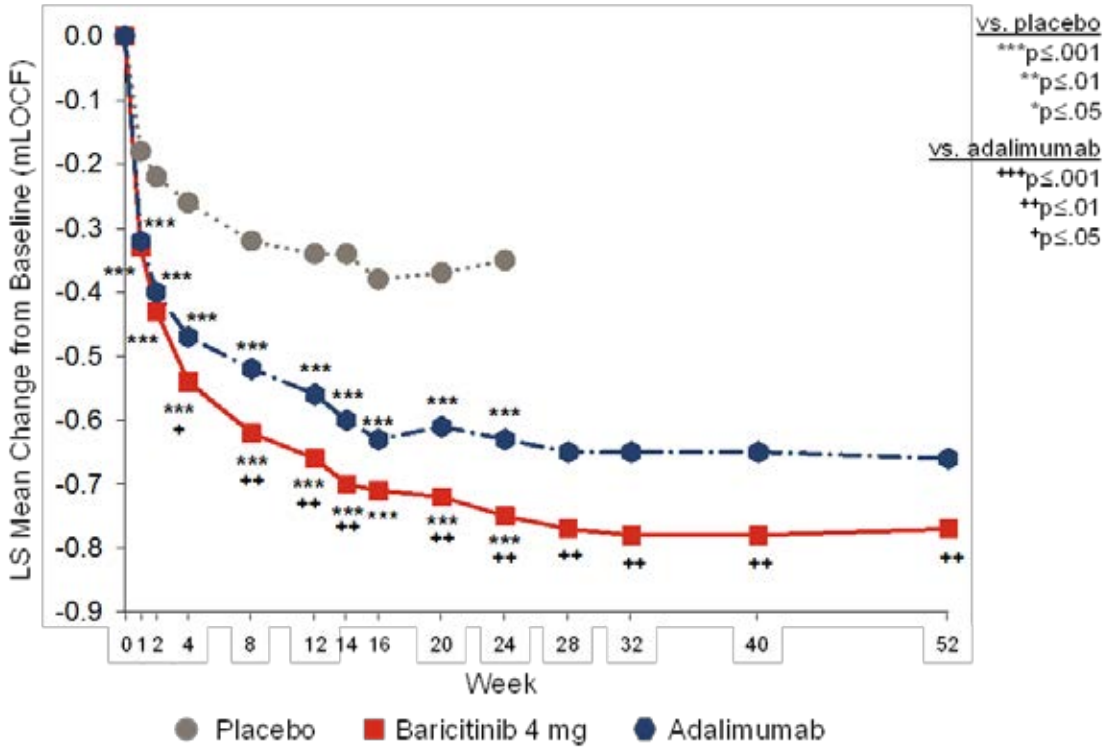


ACR20 ≥ 20% improvement in American College of Rheumatology criteria
N = number of modified intent-to-treat (mITT) patients
NRI = non-responder imputation.

Physical Function Response and Health-Related Outcomes

Treatment with OLUMIANT 4 mg, alone or in combination with cDMARDs, resulted in a statistically significant improvement in physical function compared to placebo and MTX as measured by HAQ-DI, at 12, 24 and 52 weeks. Improvements with OLUMIANT 4 mg treatment were also shown versus adalimumab at these time points. The proportion of patients achieving a clinically significant improvement (HAQ-DI improvement from baseline ≥0.30) was also higher with OLUMIANT compared to placebo or MTX at week 12 (Table 7 and 8). Improvements were seen as early as Week 1 and, in RA-BEGIN and RA-BEAM (see Figure 2), these were maintained for up to 52 weeks.

Figure 2 Change in HAQ-DI from Baseline to Week 52 in RA-BEAM (mITT, using mLOCF)



HAQ-DI = Health Assessment Questionnaire-Disability Index
N = number of modified intent-to-treat (mITT) patients
mLOCF = modified last observation carried forward

Treatment with OLUMIANT 4 mg, alone or in combination with cDMARDs, resulted in a significant improvement in pain compared to all comparators (placebo, MTX, and adalimumab), as measured on a 0-100 visual analogue scale, at 12 weeks. Greater pain reduction was seen as early as Week 1 and, in RA-BEGIN and RA-BEAM, this was maintained for up to 52 weeks.

In RA-BEAM and RA-BUILD, treatment with OLUMIANT 4 mg resulted in an improvement in the mean duration and severity of morning joint stiffness, and mean worst tiredness, compared to placebo or adalimumab as assessed using daily electronic patient diaries for 12 weeks.

In all studies, OLUMIANT-treated patients reported improvements in patient-reported quality of life, as measured by the Short Form (36) Health Survey (SF36) Physical Component Score, fatigue, as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F) and work productivity, as measured by the Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis (WPAI-RA)

Radiographic Response

The effect of OLUMIANT on progression of structural joint damage was evaluated radiographically in RA-BEGIN, RA-BEAM, and RA-BUILD and assessed using the modified Total Sharp Score (mTSS) and its components, the erosion score and joint space narrowing score.

Treatment with OLUMIANT 4 mg resulted in a statistically significant inhibition of progression of structural joint damage (Table 9). Analyses of erosion and joint space narrowing scores were consistent with the overall scores. The proportion of patients with no radiographic progression (mTSS change ≤0) was statistically significantly higher with OLUMIANT 4 mg compared to placebo at week 24.

Table 9 Radiographic Changes

Study	RA-BEGIN MTX-naïve patients			RA-BEAM MTX-IR patients			RA-BUILD cDMARD-IR patients		
Treatment group	MTX	OLU 4 mg	OLU 4 mg + MTX	PBO	OLU 4 mg	ADA 40 mg Q2W	PBO	OLU 2 mg	OLU 4 mg
N	210	159	215	488	487	330	228	229	227
Modified Total Sharp Score, mean change from baseline:									
Week 24	0.61	0.39	0.29*	0.90	0.41***	0.33***	0.70	0.33*	0.15**
Week 52	1.02	0.80	0.40**		0.71	0.60			
Erosion Score, mean change from baseline:									
Week 24	0.47	0.33	0.26*	0.61	0.29***	0.24***	0.47	0.30	0.11**
Week 52	0.81	0.55	0.34**		0.51	0.42***			
Joint Space Narrowing Score, mean change from baseline:									
Week 24	0.14	0.06	0.03	0.29	0.12**	0.10**	0.23	0.03*	0.04*
Week 52	0.21	0.25	0.06		0.21	0.19			
Proportion of patients with no radiographic progression[a]:									
Week 24	68 %	76 %	81 %**	70 %	81 %***	83 %***	74 %	72 %*	80 %**
Week 52	66 %	69 %	80 %**		79 %	81 %			

Abbreviations: ADA = adalimumab; MTX = methotrexate; OLU = Olumiant; PBO = Placebo ; MTX-IR = methotrexate inadequate responders; cDMARD -IR = conventional disease-modifying antirheumatic drug inadequate responders.

[a] No progression defined as mTSS change ≤ 0.
* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001 vs. placebo (vs. MTX for study RA-BEGIN)

OLUMIANT 4 mg vs. 2 mg

In clinical trials that included doses of 2 mg and 4 mg OLUMIANT once daily (RA-BUILD and RA-BEACON), efficacy on signs and symptoms was demonstrated with both doses. However, more consistent improvements in remission and low disease activity were seen with the 4 mg dose. The differences were most notable in the bDMARD-IR population (RA-BEACON), in which statistically significant improvements in the ACR components of swollen joint count, tender joint count and ESR were shown for OLUMIANT 4 mg compared to placebo at week 24 but not for OLUMIANT 2 mg compared to placebo. In addition, onset of efficacy was fastest and the effect size was generally largest for the 4 mg dose groups compared to 2 mg.

In a long-term extension study, patients from RA-BEAM, RA-BUILD and RA-BEACON who achieved sustained low disease activity or remission (CDAI≤10) after at least 15 months of treatment with OLUMIANT 4 mg once daily (N = 502) were re-randomised 1:1 in a double-blind manner to continue

4 mg once daily or reduce dose to 2 mg once daily. A down titration in the baricitinib dose was associated with a significant reduction in efficacy. The majority of patients maintained low disease activity or remission based on CDAI score:

- At week 12: 234/251 (93%) continuing 4 mg vs 207/251 (82%) reduced to 2 mg ($p \leq 0.001$)
- At week 24: 163/191 (85%) continuing 4 mg vs 144/189 (76%) reduced to 2 mg ($p \leq 0.05$)
- At week 48: 57/73 (78%) continuing 4 mg vs 51/86 (59%) reduced to 2 mg ($p \leq 0.05$)

The majority of patients who lost their low disease activity or remission status after dose reduction could regain disease control after the dose was returned to 4 mg.

OLUMIANT Used as Monotherapy or in Combination with Methotrexate

In RA-BEGIN, OLUMIANT 4 mg monotherapy was statistically significantly superior to methotrexate monotherapy with respect to ACR20 response rates at 24 weeks (see Table 10). Combination of OLUMIANT 4 mg with methotrexate therapy was associated with larger improvements in inflammation related measures, including ESR; correspondingly, although most patients did not exhibit radiographic progression across the treatment groups, the lowest radiographic progression rates were seen in the combination group. OLUMIANT 2 mg was not studied in this trial.

In RA-BUILD, treatment effects compared to placebo were robust whether OLUMIANT was used as monotherapy, in combination with methotrexate, or in combination with cDMARDs other than methotrexate.

DMARD-Naïve RA Patients

RA-BEGIN, a 52-week study with the planned primary analysis at week 24, evaluated 584 DMARD-naïve adult patients with moderate to severe, active RA (mean disease duration was 1.3 years) and indicators of poor prognosis, such as elevated inflammatory markers (CRP) and the presence of rheumatoid factor or anti-cyclic citrullinated peptides. This study evaluated the efficacy of OLUMIANT 4 mg monotherapy, OLUMIANT 4 mg + MTX, and MTX alone in improving the signs and symptoms of RA, physical function, and rate of progression of joint damage. The primary endpoint was the proportion of patients achieving ACR20 at week 24.

A significantly higher proportion of patients in the OLUMIANT 4 mg and OLUMIANT 4 mg + MTX groups compared to MTX alone achieved an ACR20 response at week 24: 77% versus 62% ($p = 0.003$) for OLUMIANT 4 mg monotherapy and 78% versus 62% ($p \leq 0.001$) for OLUMIANT 4 mg + MTX. The OLUMIANT 4 mg monotherapy and OLUMIANT 4 mg + MTX groups also showed statistically significant improvement compared to MTX alone across the key secondary endpoints at week 24 and 52, including ACR20, SDAI remission, and change from baseline in DAS28-hsCRP and HAQ-DI. At 52 weeks, the OLUMIANT 4 mg + MTX group showed statistically significant improvement compared to MTX as measured by mTSS and a numerically greater response in the OLUMIANT 4 mg monotherapy group compared with MTX alone. The efficacy results from RA-BEGIN are shown in Table 10.

Table 10 Efficacy Results for RA-BEGIN in DMARD-naïve Patients

			OLUMIANT 4 mg/day N=159	OLUMIANT 4 mg/day + MTX N=215	MTX N=210
Primary Endpoint					
ACR20 (%)	Week 24		77**	NA	62
Key Secondary Endpoints					
ACR (%)	Week 24	ACR20	NA	78***	62
		ACR50	60**	63***	43
		ACR70	42***	40***	21
	Week 52	ACR20	73***	73***	56
		ACR50	57***	62***	38
		ACR70	42***	46***	25
HAQ-DI (mean change from baseline)					
	Week 24		-1.04***	-1.03***	-0.74
	Week 52		-0.99***	-1.06***	-0.71
DAS28-hsCRP <2.6 response (%)					
	Week 24		40***	40***	24
	Week 52		44***	49***	24
DAS28-hsCRP ≤3.2 response (%)					
	Week 24		57***	60***	38
	Week 52		57***	63***	38
SDAI remission ≤3.3 (%)					
	Week 24		22**	23***	10
	Week 52		25**	30***	13
Radiographic Endpoints (mean change from baseline)					
	Week 52	mTSS	0.80	0.40**	1.02
		Erosion Score	0.55	0.34**	0.81
		JSN	0.25	0.06	0.21
Radiographic non-progression (%) (change from baseline in mTSS ≤0)			69	80**	66

Abbreviations: NA = Not applicable; MTX = methotrexate; ACR20 = 20% improvement in American College of Rheumatology criteria; ACR50 = 50% improvement in American College of Rheumatology criteria; ACR70 = 70% improvement in American College of Rheumatology criteria; HAQ-DI = Health Assessment Questionnaire-Disability Index; DAS28-hsCRP = Disease Activity Score 28-high-sensitivity C-reactive protein; SDAI = Simplified Disease Activity Index; mTSS = modified Total Sharp Score

** p ≤ 0.01; *** p ≤ 0.001 vs. MTX.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, baricitinib is rapidly absorbed with a median t_{max} of approximately 1 hour and an absolute bioavailability of approximately 80%. Administration with meals was not associated with a clinically relevant effect on exposure.

Distribution

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

Metabolism

Baricitinib metabolism is mediated by CYP3A4 with approximately 6% of the dose identified as undergoing biotransformation. No metabolites were quantifiable in plasma. Baricitinib was excreted predominately as unchanged drug in urine (69%) and faeces (15%) and only 4 minor oxidative metabolites (3 in urine, 1 in faeces) were identified.

Excretion

Renal elimination is the principal mechanism for baricitinib's clearance through glomerular filtration and active secretion via OAT3, Pgp, BCRP and MATE2-K. 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 faeces.

Mean apparent clearance (CL/F) and half-life in patients with rheumatoid arthritis was 9.42 L/hr (CV = 34.3%) and 12.5 hours (CV = 27.4%), respectively. C_{max} and AUC at steady state were 1.4- and 2.0 fold higher, respectively, in patients with RA compared to healthy subjects.

Other Intrinsic Factors

Body weight, sex, race, and ethnicity did not have a clinically relevant effect on the pharmacokinetics (PK) of baricitinib. The mean effects of intrinsic factors on PK parameters (AUC and C_{max}) were generally within the intersubject PK variability of baricitinib. Therefore, no dose adjustment is needed based on these patient factors.

Renal Impairment

Renal function was found to significantly affect baricitinib exposure. Subjects with moderate, Stage 3 renal impairment (GFR 30 - ≤60 mL/min/1.73m$^{2)}$ and severe, Stage 4 & 5 renal impairment (GFR <30 mL/min/1.73m^2) have approximately 2-fold and 4-fold increases, respectively, in baricitinib AUC values compared to subjects with normal renal function.

The recommended dose of OLUMIANT in patients with estimated GFR of 30 - ≤60 mL/min/1.73 m^2 is 2 mg once daily. OLUMIANT is not recommended for use in patients with estimated GFR of <30 mL/min/1.73 m^2.

Hepatic Impairment

There was no clinically relevant effect on the PK of baricitinib in patients with mild or moderate hepatic impairment. No dose adjustment is necessary in these patients. The use of OLUMIANT has not been studied in patients with severe hepatic impairment and is therefore not recommended.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Baricitinib was not genotoxic in bacterial reverse mutagenicity assays (Ames assay), in the in vitro human peripheral blood lymphocyte chromosomal aberration assay, or in the in vivo micronucleus assay in the rat. All assays were validated by the use of appropriate controls. The overall risk of genotoxicity is considered to be low.

Carcinogenicity

Baricitinib did not produce neoplastic changes in two year rat and six month transgenic mouse carcinogenicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

croscarmellose sodium
magnesium stearate
mannitol
microcrystalline cellulose
iron oxide red
lecithin
macrogol 3350
polyvinyl alcohol
purified talc
titanium dioxide

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Stored below 30°C. Store in the original package

6.5 NATURE AND CONTENTS OF CONTAINER

OLUMIANT is available as debossed, film-coated, immediate-release tablets in PVC/PE/PCTFE (Aclar)/Al or PA/Al/PVC/Al blister packs of 7 and 28.

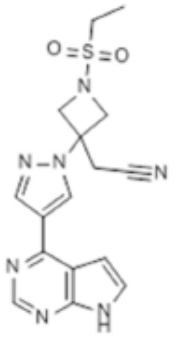
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements for disposal.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The active ingredient in OLUMIANT® tablets is baricitinib. OLUMIANT is a Janus Kinase (JAK) inhibitor with the chemical name {1-(ethylsulfonyl)-3-[4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-3-yl}acetonitrile. The empirical formula is $C_{16}H_{17}N_7O_2S$ which corresponds to a molecular weight of 371.42 daltons. The chemical structure is:



CAS number

The CAS number for baricitinib is 1187594-09-7.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Medicine

8 SPONSOR

Eli Lilly Australia Pty. Limited
112 Wharf Road, West Ryde, NSW 2114
AUSTRALIA

9 DATE OF FIRST APPROVAL

23 January 2018

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Attachment 1: Product information AusPAR AusPAR Olumiant Baricitinib Eli Lilly Australia Pty Ltd PM-2016-01468-1-3 FINAL 21 March 2019. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>

Section Changed	Summary of new information