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Baricitinib 2 mg and 4 mg Tablets
Olumiant™

1. NAME OF THE MEDICINAL PRODUCT

Baricitinib 2 mg and 4 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Olumiant™ 2 mg film-coated tablets

Each tablet contains Baricitinib 2mg, Intragranular (Mannitol USP-NF 52 mg, Microcrystalline Cellulose USP-NF 92 mg, Croscarmellose Sodium USP-NF 6mg, Magnesium Stearate USP-NF 0.6 mg), Extragranular (Microcrystalline Cellulose USP-NF 40 mg, Croscarmellose Sodium USP-NF 6 mg, Magnesium Stearate USP-NF 1.4 mg), Color Mixture- Pink 85G140008, Color Mixture- Pink 85G140009

Olumiant™ 4 mg film-coated tablets

Each tablet contains Baricitinib 4mg, Intragranular (Mannitol USP-NF 50 mg, Microcrystalline Cellulose USP-NF 92 mg, Croscarmellose Sodium USP-NF 6mg, Magnesium Stearate USP-NF 0.6 mg), Extragranular (Microcrystalline Cellulose USP-NF 40 mg, Croscarmellose Sodium USP-NF 6 mg, Magnesium Stearate USP-NF 1.4 mg), Color Mixture- Pink 85G140008, Color Mixture- Pink 85G140009

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Olumiant™ 2 mg film-coated tablets

Light pink, 9.0 x 7.5 mm oblong tablets, debossed with "Lilly" on one side and "2" on the other.

Olumiant™ 4 mg film-coated tablets

Medium pink, 8.5 mm round tablets, debossed with "Lilly" on one side and "4" on the other.

The tablets contain a recessed area on each side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Baricitinib is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs. Baricitinib may be used as monotherapy or in combination with methotrexate (see sections 4.4, 4.5 and 5.1 for available data on different combinations).

4.2 Dosage and method of administration

Treatment should be initiated by physicians experienced in the diagnosis and treatment of rheumatoid arthritis.

Dosage

The recommended dose of Olumiant™ is 4 mg once daily. A dose of 2 mg once daily is appropriate for patients such as those aged ≥ 75 years and may be appropriate for patients with a history of chronic or recurrent infections. 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 (see section 5.1).

Treatment should not be initiated in patients with an absolute lymphocyte count (ALC) less than 0.5 x 10^9 cells/L, an absolute neutrophil count (ANC) less than 1 x 10^9 cells/L, or who have a haemoglobin value less than 8 g/dL. Treatment may be initiated once values have improved above these limits (see section 4.4).

Renal impairment

The recommended dose is 2 mg once daily in patients with creatinine clearance between 30 and 60 mL/min. Olumiant™ is not recommended for use in patients with creatinine clearance < 30 mL/min (see section 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. Olumiant™ is not recommended for use in patients with severe hepatic impairment (see section 5.2).

Co-administration with OAT3 inhibitors

The recommended dose is 2 mg once daily in patients taking Organic Anion Transporter 3 (OAT3) inhibitors with a strong inhibition potential, such as probenecid (see section 4.5).

Elderly

Clinical experience in patients ≥ 75 years is very limited and in these patients a starting dose of 2 mg is appropriate.

Paediatric population

The safety and efficacy of Olumiant™ in children and adolescents aged 0 to 18 years have not yet been established. No data are available.

Method of administration

Oral use.

Olumiant™ is to be taken once daily with or without food and may be taken at any time of the day.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Infections

Baricitinib is associated with an increased rate of infections such as upper respiratory tract infections compared to placebo (see section 4.8). In treatment naïve patients, combination with methotrexate resulted in increased frequency of infections compared to baricitinib monotherapy. The risks and benefits of treatment with Olumiant™ should be carefully considered prior to initiating therapy in patients with active, chronic or recurrent infections (see section 4.2). If an infection develops, the patient should be monitored carefully and Olumiant™ therapy should be temporarily interrupted if the patient is not responding to standard therapy. Olumiant™ treatment should not be resumed until the infection resolves.

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.

Haematological abnormalities

Absolute Neutrophil Count (ANC) < 1 x 10^9 cells/L, Absolute Lymphocyte Count (ALC) < 0.5 x 10^9 cells/L and haemoglobin < 8 g/dL were reported in less than 1 % of patients in clinical trials. Treatment should not be initiated, or should be temporarily interrupted, in patients with an ANC < 1 x 10^9 cells/L, ALC < 0.5 x 10^9 cells/L or haemoglobin < 8 g/dL observed during routine patient management (see section 4.2).

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

Viral reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster, herpes simplex), were reported in clinical studies (see section 4.8). Herpes zoster was reported more commonly in patients ≥ 65 years of age who had previously been treated with both biologic and conventional DMARDs. If a patient develops herpes zoster, Olumiant™ treatment should be temporarily interrupted until the episode resolves.

Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with Olumiant™. 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 allowed to participate. Patients with hepatitis B surface antibody and hepatitis B core antibody, without hepatitis B surface antigen, were also allowed to participate; such patients should be monitored for expression of hepatitis B virus (HBV) DNA. If HBV DNA is detected, a liver specialist should be consulted to determine if treatment interruption is warranted.

Vaccination

No data are available on the response to vaccination with live vaccines in patients receiving baricitinib. Use with live, attenuated vaccines during, or immediately prior to, Olumiant™ therapy is not recommended. Prior to initiating Olumiant™, it is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines.

Lipids

Dose dependent increases in blood lipid parameters were reported in patients treated with baricitinib compared to placebo (see section 4.8). Elevations in 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 and thereafter patients should be managed according to international clinical guidelines for hyperlipidaemia. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Hepatic transaminase elevations

Increases in alanine transaminase (ALT) and aspartate transaminase (AST) to ≥ 5 and ≥ 10 x upper limit of normal (ULN) were reported in less than 1 % of patients in clinical trials. In treatment-naïve patients, combination with methotrexate resulted in increased frequency of hepatic transaminase elevations compared with baricitinib monotherapy (see section 4.8). If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, Olumiant™ should be temporarily interrupted until this diagnosis is excluded.

Malignancy

The risk of malignancies including lymphoma is increased in patients with rheumatoid arthritis. Immunomodulatory medicinal products may increase the risk of malignancies including lymphoma. The clinical data are insufficient to assess the potential incidence of malignancies following exposure to baricitinib. Long-term safety evaluations are ongoing.

Venous Thromboembolism

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving baricitinib. Baricitinib should be used with caution in patients with risk factors for DVT/PE, such as older age, obesity, a medical history of DVT/PE, or patients undergoing surgery and immobilisation. If clinical features of DVT/PE occur, Baricitinib treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment.

Laboratory monitoring

Table 1. Laboratory measures and monitoring guidance

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

Immunosuppressive medicinal products

Combination with biologic DMARDs or other Janus kinase (JAK) inhibitors is not recommended, as a risk of additive immunosuppression cannot be excluded. Data concerning use of baricitinib with potent immunosuppressive medicinal products (e.g., azathioprine, tacrolimus, ciclosporin) are limited and caution should be exercised when using such combinations (see section 4.5).

Hypersensitivity

In post-marketing experience, cases of drug hypersensitivity associated with baricitinib administration have been reported. If any serious allergic or anaphylactic reaction occurs, baricitinib should be discontinued immediately.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Immunosuppressive medicinal products

Combination with biologic DMARDs or other JAK inhibitors has not been studied. Use of baricitinib with potent immunosuppressive medicinal products such as azathioprine, tacrolimus, or ciclosporin was limited in clinical studies of baricitinib, and a risk of additive immunosuppression cannot be excluded (see section 4.4).

Potential for other medicinal products to affect the pharmacokinetics of baricitinib

Transporters

In vitro, baricitinib is a substrate for organic anionic transporter (OAT)3, P-glycoprotein (Pgp), breast cancer resistance protein (BCRP) and multidrug and toxic extrusion protein (MATE)2-K. In a clinical pharmacology study, dosing of probenecid (an OAT3 inhibitor with strong inhibition potential) resulted in approximately a 2-fold increase in $AUC_{(0-\infty)}$ with no change in t_{max} or C_{max} of baricitinib. Consequently, the recommended dose in patients taking OAT3 inhibitors with a strong inhibition potential, such as probenecid, is 2 mg once daily (see section 4.2). No clinical pharmacology study has been conducted with OAT3 inhibitors with less inhibition potential. The prodrug leflunomide rapidly converts to teriflunomide which is a weak OAT3 inhibitor and therefore may lead to an increase in baricitinib exposure. Since dedicated interaction studies have not been conducted, caution should be used when leflunomide or teriflunomide are given concomitantly with baricitinib. Concomitant use of the OAT3 inhibitors ibuprofen and diclofenac may lead to increased exposure of baricitinib, however their inhibition potential of OAT3 is less compared to probenecid and thus a clinically relevant interaction is not expected. Coadministration of baricitinib with ciclosporin (Pgp/BCRP inhibitor) or methotrexate (substrate of several transporters including OATP1B1, OAT1, OAT3, BCRP, MRP2, MRP3, and MRP4) resulted in no clinically meaningful effects on baricitinib exposure.

Cytochrome P450 enzymes

In vitro, baricitinib is a cytochrome P450 enzyme (CYP)3A4 substrate although less than 10 % of the dose is metabolised via oxidation. In clinical pharmacology studies, coadministration of baricitinib with ketoconazole (strong CYP3A inhibitor) resulted in no clinically meaningful effect on the PK of baricitinib. Coadministration of baricitinib with fluconazole (moderate CYP3A/CYP2C19/CYP2C9 inhibitor) or rifampicin (strong CYP3A inducer) resulted in no clinically meaningful changes to baricitinib exposure.

Gastric pH modifying agents

Elevating gastric pH with omeprazole had no clinically significant effect on baricitinib exposure.

Potential for baricitinib to affect the pharmacokinetics of other medicinal products

Transporters

In vitro, baricitinib is not an inhibitor of OAT1, OAT2, OAT3, organic cationic transporter (OCT) 2, OATP1B1, OATP1B3, BCRP, MATE1 and MATE2-K at clinically relevant concentrations. Baricitinib may be a clinically relevant inhibitor of OCT1, however there are currently no known selective OCT1 substrates for which clinically significant interactions might be predicted. In clinical pharmacology studies there were no clinically meaningful effects on exposure when baricitinib was coadministered with digoxin (Pgp substrate) or methotrexate (substrate of several transporters).

Cytochrome P450 enzymes

In clinical pharmacology studies, coadministration of baricitinib with the CYP3A substrates simvastatin, ethinyl oestradiol, or levonorgestrel resulted in no clinically meaningful changes in the PK of these medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy

The JAK/STAT pathway has been shown to be involved in cell adhesion and cell polarity which can affect early embryonic development. There are no adequate data from the use of baricitinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Baricitinib was teratogenic in rats and rabbits. Animal studies indicate that baricitinib may have an adverse effect on bone development *in utero* at higher dosages.

Olumiant™ is contraindicated during pregnancy (see section 4.3). Women of childbearing potential have to use effective contraception during and for at least 1 week after treatment. If a patient becomes pregnant while taking Olumiant™ the parents should be informed of the potential risk to the foetus.

Breast-feeding

It is unknown whether baricitinib/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of baricitinib in milk (see section 5.3).

A risk to newborns/infants cannot be excluded and Olumiant™ should not be used during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue Olumiant™ therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Studies in animals suggest that treatment with baricitinib has the potential to decrease female fertility while on treatment, but there was no effect on male spermatogenesis (see section 5.3).

4.7 Effects on ability to drive and use machines

Olumiant™ has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

The most commonly reported adverse drug reactions (ADRs) occurring in ≥ 2 % of patients treated with Olumiant™ monotherapy or in combination with conventional synthetic DMARDs were increased LDL cholesterol (33.6 %), upper respiratory tract infections (14.7 %) and nausea (2.8 %). Infections reported with Olumiant™ treatment included Herpes zoster.

Tabulated list of adverse reactions

A total of 3,464 patients were treated with Olumiant™ in clinical studies in rheumatoid arthritis representing 4214 patient-years of exposure. Of these, 2166 rheumatoid arthritis patients were exposed to Olumiant™ for at least one year. Six placebo-controlled studies were integrated (997 patients on 4 mg once daily and 1070 patients on placebo) to evaluate the safety of Olumiant™ in comparison to placebo for up to 16 weeks after treatment initiation.

Table 2. Adverse Reactions

Frequency estimate: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100).

System Organ Class	Very common	Common	Uncommon
Infections and infestations	Upper respiratory tract infections[a]	Herpes zoster, Herpes simplex[b] Gastroenteritis Urinary tract infections Pneumonia	
Blood and lymphatic system disorders		Thrombocytosis >600 x 10^9 cells/L[c]	Neutropaenia <1 x 10^9 cells/L[c]
Metabolism and nutrition disorders	Hypercholesterolaemia[c]		Hypertriglyceridaemia[c]
Gastrointestinal disorders		Nausea	
Hepatobiliary disorders		ALT increased ≥3 x ULN[c]	AST increased ≥3 x ULN[c]
Skin and subcutaneous tissue disorders		Rash	Acne
Immune disorders			Swelling of the face, Urticaria
Respiratory, thoracic, mediastinal disorders			Pulmonary embolism
Vascular disorders			Deep Vein Thrombosis
Investigations			Weight increased Creatine phosphokinase increased >5 x ULN[c]

[a] Combined term (acute sinusitis, epiglottitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, tracheitis, upper respiratory tract infection).
[b] Combined term (eczema herpeticum, herpes simplex, ophthalmic herpes simplex, oral herpes).
[c] Includes changes detected during laboratory monitoring (see text below).

Description of selected adverse reactions

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.

Infections

In controlled studies, for up to 16 weeks, the incidence rate of all infections (rate of patients with ≥ 1 event per 100 patient-years of exposure) was 101 with Olumiant™ compared to 83 in the placebo group. Most infections were mild to moderate in severity. In studies which included both doses, infections were reported in 31.9%, 28.8% and 24.1% of patients up to 16 weeks in the 4 mg, 2 mg and placebo groups, respectively. Reporting rates for Olumiant™ compared to placebo for the infection-related ADRs were: Upper respiratory tract infections (14.7 % vs. 11.7 %), urinary tract infections (3.4 % vs. 2.7 %), gastroenteritis (1.6 % vs. 0.8 %), herpes simplex (1.8 % vs. 0.7 %), and herpes zoster (1.4 % vs. 0.4 %). In treatment-naïve patients, for up to 52 weeks, the frequency of upper respiratory tract infections was greater for the combination treatment of methotrexate and Olumiant™ (26.0 %) compared to methotrexate alone (22.9 %) or Olumiant™ alone (22.0 %). The rate of serious infections with Olumiant™ (1.1 %) was similar to placebo (1.2 %). For Olumiant™, the most common serious infections were herpes zoster, and cellulitis. The rate of serious infections remained stable during long term exposure. The overall incidence rate of serious infections in the clinical trial programme was 3.2 per 100 patient-years.

Hepatic transaminase elevations

In controlled studies, for up to 16 weeks, alanine transaminase (ALT) and aspartate transaminase (AST) elevations ≥ 3 x upper limit of normal (ULN) were observed in 1.4 % and 0.8 % of patients treated with Olumiant™, compared to 1.0 % and 0.8 % respectively of patients treated with placebo. Most cases of hepatic transaminase elevations were asymptomatic and transient.

In treatment-naïve patients, the combination of Olumiant™ with potentially hepatotoxic medicinal products, such as methotrexate, resulted in increased frequency of these elevations. For up to 52 weeks, the frequency of ALT and AST elevations ≥ 3 x ULN were greater for the combination treatment of methotrexate and Olumiant™ (7.5 % and 3.8 %) compared to methotrexate alone (2.9 % and 0.5 %) or Olumiant™ alone (1.9 % and 1.3 %).

The pattern and incidence of elevation in ALT/AST remained stable over time including in the long-term extension study.

Lipid elevations

Baricitinib treatment was associated with dose-dependent increases in lipid parameters including total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol. There was no change in the LDL/HDL ratio. Elevations were observed at 12 weeks and remained stable thereafter at a higher value than baseline including in the long-term extension study. In controlled studies, for up to 16 weeks, the following rates were observed for Olumiant™ vs. placebo:

- Increased total cholesterol ≥ 5.17 mmol/L: 49.1 % vs.15.8 %, respectively
- Increased LDL cholesterol ≥ 3.36 mmol/L: 33.6 % vs. 10.3 %, respectively
- Increased HDL cholesterol ≥ 1.55 mmol/L: 42.7 % vs. 13.8 %, respectively
- Increased triglycerides ≥ 5.65 mmol/L: 0.4 % vs. 0.5 %, respectively

In studies which included both doses, a dose-relationship was observed with increased total cholesterol ≥ 5.17 mmol/L reported in 48.8 %, 34.7 % and 17.8 % of patients up to 16 weeks in the 4 mg, 2 mg and placebo groups, respectively. Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy.

Creatine phosphokinase (CPK)

In controlled studies, for up to 16 weeks, increases in CPK values were common. Significant increases (> 5 x ULN) occurred in 0.8 % of patients treated with Olumiant™ and 0.3 % of patients treated with placebo. A dose relationship was observed with CPK elevations ≥ 5 x ULN of normal reported in 1.5 %, 0.8 % and 0.6 % of patients at 16 weeks in the 4 mg, 2 mg and placebo groups, respectively. Most cases were transient and did not require treatment discontinuation. In clinical trials, there were no confirmed cases of rhabdomyolysis. Elevations of CPK were observed at 4 weeks and remained stable at a higher value than baseline thereafter including in the long-term extension study.

Neutropaenia

In controlled studies, for up to 16 weeks, decreases in neutrophil counts below 1 x 10^9 cells/L occurred in 0.3 % of patients treated with Olumiant™ compared to 0 % of patients treated with placebo. There was no clear relationship between decreases in neutrophil counts and the occurrence of serious infections. However, in clinical studies, treatment was interrupted in response to ANC < 1 x 10^9 cells/L. The pattern and incidence of decreases in neutrophil counts remained stable at a lower value than baseline over time including in the long-term extension study.

Thrombocytosis

In controlled studies, for up to 16 weeks, increases in platelet counts above 600 x 10^9 cells/L occurred in 2.0 % of patients treated with Olumiant™ 4 mg and 1.1 % of patients treated with placebo. No association was observed between increased platelet counts and adverse events of a thrombotic nature. The pattern and incidence of increases in platelet counts remained stable at a higher value than baseline over time including in the long term extension study.

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-limiting toxicity. Adverse events were comparable to those seen at lower doses and no specific toxicities were identified. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AA37

Mechanism of action

Baricitinib is a selective and reversible inhibitor of Janus kinase (JAK)1 and JAK2. In isolated enzyme assays, baricitinib inhibited the activities of JAK1, JAK2, Tyrosine Kinase 2 and JAK3 with IC_{50} values of 5.9, 5.7, 53 and > 400 nM, respectively.

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. Baricitinib modulates these signalling pathways by partially inhibiting JAK1 and JAK2 enzymatic activity, thereby reducing the phosphorylation and activation of STATs.

Pharmacodynamic effects

Inhibition of IL-6 induced STAT3 phosphorylation

Administration of baricitinib 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.

Immunoglobulins

Mean serum IgG, IgM, and IgA values decreased by 12 weeks after starting treatment with Olumiant™, and remained stable at a lower value than baseline through at least 104 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 1 week after starting treatment with Olumiant™ and were maintained throughout dosing.

Item Code PA007SPIN01	**Previous Item Code** *(to be destroyed)* PA007SPIN00

PPD Information Box

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ALRP Information Box

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exp date: N/A
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Operator name: KP Time: 09:17

Creatinine

Baricitinib induced a mean increase in serum creatinine levels of 3.8 µmol/L after two weeks of treatment, as compared to placebo, which remained stable thereafter during up to 104 weeks of treatment. This may be due to inhibition of creatinine secretion by baricitinib in the renal tubules. Consequently, estimates of the glomerular filtration rate based on serum creatinine may be slightly reduced, without actual loss of renal function or the occurrence of renal adverse events.

Vaccine Study

The influence of baricitinib on the humoral response to non-live vaccines was evaluated in 106 RA patients under stable treatment with baricitinib 2 or 4 mg, receiving inactivated pneumococcal or tetanus vaccination. The majority of these patients (n = 94) were co-treated with methotrexate. For the total population, pneumococcal vaccination resulted in a satisfactory IgG immune response in 68.0 % (95 % CI: 58.4 %, 76.2 %) of the patients. In 43.1 % (95 % CI: 34.0 %, 52.8 %) of the patients, a satisfactory IgG immune response to tetanus vaccination was achieved.

Clinical efficacy

The efficacy and safety of Olumiant™ once daily was assessed in 4 Phase III randomised, double-blind, multicentre studies in patients with moderate to severe active rheumatoid arthritis diagnosed according to the ACR/EULAR 2010 criteria (see Table 3). Patients over 18 years of age were eligible to participate. The presence of at least 6 tender and 6 swollen joints was required 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.

The RA-BEGIN Study in MTX-naïve patients is supportive for the target population of patients with an inadequate response to, or intolerance to, other DMARDs (section 4.1).

Table 3. Clinical Trial Summary

Study name (Duration)	**Population** (Number)	**Treatment arms**	**Summary of key outcome measures**
RA-BEGIN (52 weeks)	MTX-naïve[1] (584)	• Olumiant™ 4 mg QD • Olumiant™ 4 mg QD + MTX • MTX	• Primary endpoint: ACR20 at week 24 • Physical function (HAQ-DI) • Radiographic progression (mTSS) • Low disease activity and Remission (SDAI)
RA-BEAM (52 weeks)	MTX-IR[2] (1305)	• Olumiant™ 4 mg QD • Adalimumab 40 mg SC Q2W • Placebo All patients on background MTX	• Primary endpoint:ACR20 at week 12 • Physical function (HAQ-DI) • Radiographic progression (mTSS) • Low disease activity and Remission (SDAI) • Morning Joint Stiffness
RA-BUILD (24 weeks)	cDMARD-IR[3] (684)	• Olumiant™ 4 mg QD • Olumiant™ 2 mg QD • Placebo On background cDMARDs[5] if on stable cDMARD at study entry	• Primary endpoint: ACR20 at week 12 • Physical function (HAQ-DI) • Low disease activity and remission (SDAI) • Radiographic progression (mTSS) • Morning Joint Stiffness
RA-BEACON (24 weeks)	TNF-IR[4] (527)	• Olumiant™ 4 mg QD • Olumiant™ 2 mg QD • Placebo On background cDMARDs[5]	• Primary endpoint: ACR20 at week 12 • Physical function (HAQ-DI) • Low disease activity and Remission (SDAI)

Abbreviations: QD = Once daily; Q2W = Once every 2 weeks; SC = Subcutaneously; ACR = American College of Rheumatology; SDAI = Simplified Disease Activity Index; HAQ-DI = Health Assessment Questionnaire-Disability Index; mTSS = modified Total Sharp Score

[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-naïve

[3] Patients who had an inadequate response or were intolerant to ≥ 1 cDMARDs; biologic- naïve

[4] Patients who had an inadequate response or were intolerant to ≥ 1 bDMARDs; including at least one TNF inhibitor

[5] Most common concomitant cDMARDs included MTX, hydroxychloroquine, leflunomide and sulfasalazine

Clinical Response

In all studies, patients treated with Olumiant™ 4 mg once daily had statistically significantly higher ACR20, ACR50 and ACR70 response at 12 weeks compared to placebo, MTX or adalimumab (see Table 4).Time to onset of efficacy was rapid across measures with significantly 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™ resulted in significant improvement in patient and physician global assessments, HAQ-DI, pain assessment and CRP at Weeks 12, 24 and 52 compared to adalimumab.

In placebo-controlled trials in which MTX was not required, 501 subjects randomized to baricitinib 2 mg or 4 mg received MTX as background therapy, and 303 received conventional DMARDs other than MTX (approximately half with MTX and half without). The most common concomitant 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 baricitinib.

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 SDAI ≤ 3.3 and CDAI ≤ 2.8, at weeks 12 and 24 (Table 4).

In all 4 studies, a significantly higher proportion of patients treated with Olumiant™ 4 mg compared to placebo or MTX achieved low disease activity or remission (DAS28-ESR or 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 4: Response, Remission and Physical Function

Study	**RA-BEGIN** MTX-naïve patients			**RA-BEAM** MTX-IR patients			**RA-BUILD** cDMARD-IR patients			**RA-BEACON** TNF-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	PBO	OLU 2 mg	OLU 4 mg
N	210	159	215	488	487	330	228	229	227	176	174	177
ACR20:												
Week 12	59 %	79 %***	77 %***	40 %	70 %***†	61 %***	39 %	66 %***	62 %***	27 %	49 %***	55 %***
Week 24	62 %	77 %**	78 %***	37 %	74 %***†	66 %***	42 %	61 %***	65 %***	27 %	45 %***	46 %***
Week 52	56 %	73 %***	73 %***		71 %††	62 %						
ACR50:												
Week 12	33 %	55 %***	60 %***	17 %	45 %***††	35 %***	13 %	33 %***	34 %***	8 %	20 %**	28 %***
Week 24	43 %	60 %**	63 %***	19 %	51 %***	45 %***	21 %	41 %***	44 %***	13 %	23 %*	29 %***
Week 52	38 %	57 %***	62 %***		56 %†	47 %						
ACR70:												
Week 12	16 %	31 %***	34 %***	5 %	19 %***†	13 %***	3 %	18 %***	18 %***	2 %	13 %***	11 %**
Week 24	21 %	42 %***	40 %***	8 %	30 %***†	22 %***	8 %	25 %***	24 %***	3 %	13 %***	17 %***
Week 52	25 %	42 %***	46 %***		37 %	31 %						
DAS28-hsCRP ≤ 3.2:												
Week 12	30 %	47 %***	56 %***	14 %	44 %***††	35 %***	17 %	36 %***	39 %***	9 %	24 %***	32 %***
Week 24	38 %	57 %***	60 %***	19 %	52 %***	48 %***	24 %	46 %***	52 %***	11 %	20 %*	33 %***
Week 52	38 %	57 %***	63 %***		56 %†	48 %						
DAS28-ESR ≤ 3.2:												
Week 12	15 %	21 %	34 %***	7 %	24 %***	21 %***	7 %	21 %***	22 %***	4 %	13 %**	12 %**
Week 24	23 %	36 %**	39 %***	10 %	32 %***	34 %***	10 %	29 %***	32 %***	7 %	11 %	17 %**
Week 52	27 %	36 %	45 %***		39 %	36 %						
SDAI ≤ 3.3:												
Week 12	6 %	14 %*	20 %***	2 %	8 %***	7 %***	1 %	9 %***	9 %***	2 %	2 %	5 %
Week 24	10 %	22 %**	23 %***	3 %	16 %***	14 %***	4 %	17 %***	15 %***	2 %	5 %	9 %**
Week 52	13 %	25 %**	30 %***		23 %	18 %						
CDAI ≤ 2.8:												
Week 12	7 %	14 %*	19 %***	2 %	8 %***	7 %**	2 %	10 %***	9 %***	2 %	3 %	6 %
Week 24	11 %	21 %**	22 %**	4 %	16 %***	12 %***	4 %	15 %***	15 %***	3 %	5 %	9 %*
Week 52	16 %	25 %*	28 %**		22 %	18 %						
HAQ-DI Minimum Clinically Important Difference (decrease in HAQ-DI score of ≥ 0.30):												
Week 12	60 %	81 %***	77 %***	46 %	68 %***	64 %***	44 %	60 %***	56 %**	35 %	48 %*	54 %***
Week 24	66 %	77 %*	74 %	37 %	67 %***†	60 %***	37 %	58 %***	55 %***	24 %	41 %***	44 %***
Week 52	53 %	65 %*	67 %**		61 %	55 %						

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

Abbreviations: ADA = adalimumab; MTX = methotrexate; OLU = Olumiant™; PBO = Placebo

* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001 vs. placebo (vs. MTX for study RA-BEGIN)

† p ≤ 0.05; †† p ≤ 0.01; ††† p ≤ 0.001 vs. adalimumab

Radiographic response

The effect of Olumiant™ on progression of structural joint damage was evaluated radiographically in studies 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 5). 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 significantly higher with Olumiant™ 4 mg compared to placebo at weeks 24 and 52.

Table 5. 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[a]	OLU 4 mg	ADA 40 mg Q2W	PBO	OLU 2 mg	OLU 4 mg
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**	1.80	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**	1.23	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	0.58	0.21***	0.19**			
Proportion of patients with no radiographic progression[b]:									
Week 24	68 %	76 %	81 %**	70 %	81 %***	83 %***	74 %	72 %	80 %
Week 52	66 %	69 %	80 %**	70 %	79 %**	81 %**			

Abbreviations: ADA = adalimumab; MTX = methotrexate; OLU = Olumiant™; PBO = Placebo

[a] Placebo data at week 52 derived using linear extrapolation

[b] No progression defined as mTSS change ≤ 0.

* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001 vs. placebo (vs. MTX for study RA-BEGIN)

Physical function response and health-related outcomes

Treatment with Olumiant™ 4 mg, alone or in combination with cDMARDs, resulted in a significant improvement in physical function compared to all comparators (placebo, MTX, adalimumab), as measured by HAQ-DI, at 12, 24 and 52 weeks. The proportion of patients achieving a clinically significant improvement (HAQ-DI ≥ 0.30) was also higher with Olumiant™ compared to placebo or MTX at week 12 (Table 4). Improvements were seen as early as Week 1 and, in studies RA-BEGIN and RA-BEAM, this was maintained for up to 52 weeks.

Treatment with Olumiant™ 4 mg, alone or in combination with cDMARDs, resulted in a significant improvement in pain compared to all comparators (placebo, MTX, adalimumab), as measured on a 0-100 visual analogue scale, at 12 weeks. Statistically significant pain reduction was seen as early as Week 1 and in studies 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 a significant improvement in the mean duration and severity of morning joint stiffness 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 (SF-36) Physical Component Score and fatigue, as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F).

Olumiant™ 4 mg vs. 2 mg

Differences in efficacy between the 4 mg and the 2 mg doses 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, for both study RA-BEACON and RA-BUILD, onset of efficacy was faster and the effect size was generally larger for the 4 mg dose groups compared to 2 mg.

In a long-term extension study, patients from Studies 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 were re-randomized 1:1 in a double-blind manner to continue 4 mg once daily or reduce dose to 2 mg once daily. 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 ≤ 0.001)
- At week 24: 163/191 (85 %) continuing 4 mg vs. 144/189 (76 %) reduced to 2 mg (p ≤ 0.05)
- At week 48: 57/73 (78 %) continuing 4 mg vs. 51/86 (59 %) reduced to 2 mg (p ≤ 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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Olumiant™ in one or more subsets of the paediatric population in chronic idiopathic arthritis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Following oral administration of baricitinib, a dose-proportional increase in systemic exposure was observed in the therapeutic dose range. The PK of baricitinib is linear with respect to time.

Absorption

Following oral administration, baricitinib is rapidly absorbed with a median t_{max} of approximately 1 hour (range 0.5 - 3.0 h) and an absolute bioavailability of approximately 79 % (CV = 3.94 %). Food intake led to a decreased exposure by up to 14 %, a decrease in C_{max} by up to 18 % and delayed t_{max} by 0.5 hours. 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.

Biotransformation

Baricitinib metabolism is mediated by CYP3A4, with less than 10 % of the dose identified as undergoing biotransformation. No metabolites were quantifiable in plasma. In a clinical pharmacology study, baricitinib was excreted predominately as the unchanged active substance in urine (69 %) and faeces (15 %) and only 4 minor oxidative metabolites were identified (3 in urine; 1 in faeces) constituting approximately 5 % and 1 % of the dose, respectively. *In vitro*, baricitinib is a substrate for CYP3A4, OAT3, Pgp, BCRP and MATE2-K, and may be a clinically relevant inhibitor of the transporter OCT1 (see section 4.5). Baricitinib is not an inhibitor of the transporters OAT1, OAT2, OAT3, OCT2, OATP1B1, OATP1B3, BCRP, MATE1 and MATE2-K at clinically relevant concentration.

Elimination

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 hrs (CV = 27.4 %), respectively. C_{max} and AUC at steady state are 1.4- and 2.0–fold higher, respectively, in subjects with rheumatoid arthritis compared to healthy subjects.

Renal Impairment

Renal function was found to significantly affect baricitinib exposure. The mean ratios of AUC in patients with mild and moderate renal impairment to patients with normal renal function are 1.41 (90 % CI: 1.15-1.74) and 2.22 (90 % CI: 1.81-2.73), respectively. The mean ratios of C_{max} in patients with mild and moderate renal impairment to patients with normal renal function are 1.16 (90 %CI: 0.92-1.45) and 1.46 (90 %CI: 1.17-1.83), respectively. See section 4.2 for dose recommendations.

Hepatic Impairment

There was no clinically relevant effect on the PK of baricitinib in patients with mild or moderate hepatic impairment. The use of baricitinib has not been studied in patients with severe hepatic impairment.

Elderly

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

Paediatric population

The safety, efficacy and pharmacokinetics of baricitinib have not yet been established in a paediatric population (see section 4.2).

Other intrinsic Factors

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.

Decreases in lymphocytes, eosinophils and basophils as well as lymphoid depletion in organs/tissues of the immune system were observed in mice, rats and dogs. Opportunistic infections related to demodicosis (mange) were observed in dogs at exposures approximately 7 times the human exposure. Decreases in red blood cell parameters were observed in mice, rats and dogs at exposures approximately 6 to 36 times the human exposure. Degeneration of the sternal growth plate was observed in some dogs, at low incidence and also in control animals, but with a dose-effect relationship regarding severity. At present it is not known whether this is clinically relevant.

In rat and rabbit reproductive toxicology studies, baricitinib was shown to reduce foetal growth/weight and produce skeletal malformations (at exposures of approximately 10 and 39 times the human exposure, respectively). No adverse foetal effects were observed at exposures 2 times the human exposure based on AUC.

In a combined male/female rat fertility study, baricitinib decreased overall mating performance (decreased fertility and conception indices). In female rats there were decreased numbers of corpora lutea and implantation sites, increased pre-implantation loss, and/or adverse effects on intrauterine survival of the embryos. 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 was detected in the milk of lactating rats. In a pre- and postnatal development study, decreased pup weights and decreased postnatal survival were observed at exposures 4 and 21 times, respectively, the human exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores

- cellulose, microcrystalline
- croscarmellose sodium
- magnesium stearate
- mannitol

Film coating

- Titanium Dioxide
- Titanium Oxide
- Polyethylene Glycol
- Macrogol 4000
- lecithin (soya) and Soybean Lecithin
- Ferric Oxide
- Red ferric Oxide
- Macrogol
- Polyvinyl alcohol) and Partially Hydrolyzed Polyvinyl Alcohol
- Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Alu/Alu blisters in 1 carton of 7 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

7. Manufactured By:

Lilly, S.A., Avda. de la Industria, 30
28108 Alcobendas, Madrid, Spain

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