ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

Olumiant 2 mg film-coated tablets
Olumiant 4 mg 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.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Olumiant 2 mg film-coated tablets

Light pink, 9 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

Rheumatoid arthritis

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).

Atopic dermatitis

Baricitinib is indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy.

4.2 Posology and method of administration

Treatment should be initiated by physicians experienced in the diagnosis and treatment of the conditions for which this medicinal product is indicated.
Posology

**Rheumatoid arthritis**
The recommended dose of baricitinib 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).

**Atopic dermatitis**
The recommended dose of baricitinib 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 should 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).

Baricitinib can be used with or without topical corticosteroids. The efficacy of baricitinib can be enhanced when given with topical corticosteroids (see section 5.1). Topical calcineurin inhibitors may be used, but should be reserved for sensitive areas only, such as the face, neck, intertriginous and genital areas.

Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit after 8 weeks of treatment.

**Treatment initiation**
Treatment should not be initiated in patients with an absolute lymphocyte count (ALC) less than 0.5 x 10⁹ cells/L, an absolute neutrophil count (ANC) less than 1 x 10⁹ 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).

**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).

**Special populations**

**Renal impairment**
The recommended dose is 2 mg once daily in patients with creatinine clearance between 30 and 60 mL/min. Baricitinib 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. Baricitinib is not recommended for use in patients with severe hepatic impairment (see section 5.2).

**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 baricitinib in children and adolescents aged 0 to 18 years have not yet been established. No data are available.
Method of administration

Oral use.

Baricitinib 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 rheumatoid arthritis clinical studies, combination with methotrexate resulted in increased frequency of infections compared to baricitinib monotherapy.

The risks and benefits of treatment with baricitinib 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 therapy should be temporarily interrupted if the patient is not responding to standard therapy. Treatment should not be resumed until the infection resolves.

Tuberculosis

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

Haematological abnormalities

Absolute Neutrophil Count (ANC) < 1 x 10^9 cells/L and Absolute Lymphocyte Count (ALC) < 0.5 x 10^9 cells/L were reported in clinical trials. Haemoglobin < 8 g/dL was reported in rheumatoid arthritis 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). In rheumatoid arthritis clinical studies, herpes zoster was reported more commonly in patients ≥ 65 years of age who had previously been treated with both biologic and conventional disease-modifying antirheumatic drugs (DMARDs). If a patient develops herpes zoster, 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 baricitinib. 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 baricitinib therapy is not recommended. Prior to initiating treatment, 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 (see section 4.8). 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 therapy and thereafter patients should be managed according to international clinical guidelines for hyperlipidaemia.

**Hepatic transaminase elevations**

Dose dependent increases in blood alanine transaminase (ALT) and aspartate transaminase (AST) activity were reported in patients treated with baricitinib (see section 4.8).

Increases in ALT and AST to ≥ 5 and ≥ 10 x upper limit of normal (ULN) were reported in clinical trials. In rheumatoid arthritis clinical studies, 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, treatment 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**

Cases of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving baricitinib (see section 4.8). 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, treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment.
Laboratory monitoring

Table 1. Laboratory measures and monitoring guidance

<table>
<thead>
<tr>
<th>Laboratory Measure</th>
<th>Action</th>
<th>Monitoring guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid parameters</td>
<td>Patients should be managed according to international clinical guidelines for hyperlipidaemia</td>
<td>12 weeks after initiation of treatment and thereafter according to international clinical guidelines for hyperlipidaemia</td>
</tr>
<tr>
<td>Absolute Neutrophil Count (ANC)</td>
<td>Treatment should be interrupted if ANC &lt; 1 x 10⁹ cells/L and may be restarted once ANC return above this value</td>
<td>Before treatment initiation and thereafter according to routine patient management</td>
</tr>
<tr>
<td>Absolute Lymphocyte Count (ALC)</td>
<td>Treatment should be interrupted if ALC &lt; 0.5 x 10⁹ cells/L and may be restarted once ALC return above this value</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (Hb)</td>
<td>Treatment should be interrupted if Hb &lt; 8 g/dL and may be restarted once Hb return above this value</td>
<td></td>
</tr>
<tr>
<td>Hepatic transaminases</td>
<td>Treatment should be temporarily interrupted if drug-induced liver injury is suspected</td>
<td></td>
</tr>
</tbody>
</table>

Immunosuppressive medicinal products

Combination with biological DMARDs, biological immunomodulators or other Janus kinase (JAK) inhibitors is not recommended, as a risk of additive immunosuppression cannot be excluded.

In rheumatoid arthritis, 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).

In atopic dermatitis, combination with ciclosporin or other potent immunosuppressants has not been studied and is not recommended (see section 4.5).

Hypersensitivity

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

Diverticulitis

Cases of diverticulitis and gastrointestinal perforation have been reported in clinical trials and from postmarketing sources (see section 4.8). Baricitinib should be used with caution in patients with diverticular disease and especially in patients chronically treated with concomitant medicinal products associated with an increased risk of diverticulitis: nonsteroidal anti-inflammatory drugs, corticosteroids, and opioids. Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of diverticulitis or gastrointestinal perforation.
Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Immunosuppressive medicinal products

Combination with biological DMARDs, biological immunomodulators or other JAK inhibitors has not been studied. In rheumatoid arthritis, use of baricitinib with potent immunosuppressive medicinal products such as azathioprine, tacrolimus, or ciclosporin was limited in clinical studies, and a risk of additive immunosuppression cannot be excluded. In atopic dermatitis, combination with ciclosporin or other potent immunosuppressants has not been studied and is not recommended (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-∞) with no change in tmax or Cmax 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 doses.

Baricitinib 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 baricitinib 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 baricitinib should not be used during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue 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
Baricitinib 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 reactions with baricitinib are increased LDL cholesterol (25.1%), upper respiratory tract infections (16.7%), headache (4.9%), herpes simplex (3.7%), and urinary tract infections (2.7%). Serious pneumonia and serious herpes zoster occurred uncommonly in patients with rheumatoid arthritis.

Tabulated list of adverse reactions
Frequency estimate: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000). The frequencies in Table 2 are based on integrated data from clinical trials and/or postmarketing setting across both rheumatoid
arthritis and atopic dermatitis indications unless stated otherwise; where notable differences in frequency are observed in one indication alone, these are presented in the footnotes below the table.

Table 2. Adverse reactions

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infections</td>
<td>Herpes zoster&lt;sup&gt;b&lt;/sup&gt; Herpes simplex Gastroenteritis Urinary tract infections Pneumonia&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Neutropena &lt; 1 x 10&lt;sup&gt;9&lt;/sup&gt; cells/L&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Thrombocytosis &gt; 600 x 10&lt;sup&gt;9&lt;/sup&gt; cells/L&lt;sup&gt;a,d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune disorders</td>
<td></td>
<td>Swelling of the face, Urticaria</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hypercholesterolaemia&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>Hypertriglyceridaemia&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td>Deep Vein Thrombosis</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic, mediastinal disorders</td>
<td></td>
<td>Pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea&lt;sup&gt;d&lt;/sup&gt; Abdominal pain</td>
<td>Diverticulitis</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>ALT increased ≥ 3 x ULN&lt;sup&gt;a,d&lt;/sup&gt;</td>
<td>AST increased ≥ 3 x ULN&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash Acne&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Creatine phosphokinase increased &gt; 5 x ULN&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>Weight increased</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes changes detected during laboratory monitoring (see text below).
<sup>b</sup> Frequency for herpes zoster is based on rheumatoid arthritis clinical trials.
<sup>c</sup>In rheumatoid arthritis clinical trials, the frequency of acne and creatine phosphokinase increased > 5 x ULN was uncommon.
<sup>d</sup> In atopic dermatitis clinical trials, the frequency of pneumonia, thrombocytosis > 600 x 10<sup>9</sup> cells/L, nausea, and ALT ≥3 x ULN was uncommon.

Description of selected adverse reactions

**Gastrointestinal disorders**

In rheumatoid arthritis clinical studies, in treatment-naïve patients, through 52 weeks, the frequency of nausea was greater for the combination treatment of methotrexate and baricitinib (9.3 %) compared to methotrexate alone (6.2 %) or baricitinib alone (4.4 %). In the integrated data from rheumatoid arthritis and atopic dermatitis clinical trials, nausea was most frequent during the first 2 weeks of treatment.

Cases of abdominal pain were usually mild, transient, not associated with infectious or inflammatory gastrointestinal disorders, and did not lead to treatment interruption.
Infections
In the integrated data from rheumatoid arthritis and atopic dermatitis clinical trials, most infections were mild to moderate in severity. Frequency of herpes zoster was common in rheumatoid arthritis, and very rare in atopic dermatitis. In atopic dermatitis clinical trials, there were fewer skin infections requiring antibiotic treatment with baricitinib than with placebo.

The incidence of serious infections with baricitinib was similar to placebo. The incidence 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 in rheumatoid arthritis, and 2.1 in atopic dermatitis. Serious pneumonia and serious herpes zoster occurred uncommonly in patients with rheumatoid arthritis.

Hepatic transaminase elevations
Dose dependent increases in blood ALT and AST activity were reported in studies extended over week 16. Elevations in mean ALT/AST remained stable over time. Most cases of hepatic transaminase elevations ≥ 3 x ULN were asymptomatic and transient.

In patients with rheumatoid arthritis, the combination of baricitinib with potentially hepatotoxic medicinal products, such as methotrexate, resulted in increased frequency of these elevations.

Lipid elevations
In the integrated data from rheumatoid arthritis and atopic dermatitis clinical trials, baricitinib treatment was associated with dose-dependent increases in lipid parameters including total cholesterol, LDL cholesterol, and high density lipoprotein (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 rheumatoid arthritis. Total and LDL cholesterol increased through week 52 in patients with atopic dermatitis. In rheumatoid arthritis clinical trials, baricitinib treatment was associated with dose-dependent increases in triglycerides. There was no increase in triglycerides levels in atopic dermatitis clinical trials.

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

Creatine phosphokinase (CPK)
Baricitinib treatment was associated with dose-dependent increases in CPK. Elevations of mean CPK were observed at 4 weeks and remained stable at a higher value than baseline thereafter. Across indications, most cases of CPK elevations ≥ 5 x ULN were transient and did not require treatment discontinuation.

In clinical trials, there were no confirmed cases of rhabdomyolysis.

Neutropaenia
Mean neutrophil counts decreased at 4 weeks and remained stable at a lower value than baseline over time. There was no clear relationship between neutropaenia and the occurrence of serious infections. However, in clinical studies, treatment was interrupted in response to ANC < 1 x 10⁹ cells/L.

Thrombocytosis
Increases in mean platelet counts were observed and remained stable at a higher value than baseline over time.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.
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. 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: Immunosuppressants, 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, 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, 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 and were maintained throughout dosing.

*Creatinine*
In clinical trials, baricitinib induced a mean increase in serum creatinine levels of 3.8 µmol/L after two weeks of treatment, which remained stable thereafter. 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 reactions. In atopic dermatitis, baricitinib was associated with a decrease
in cystatin C (also used to estimate glomerular filtration rate) of 0.1 mg/L at week 4, with no further decrease noted up to week 16.

In vitro skin models
In an in-vitro human skin model treated with pro-inflammatory cytokines (i.e., IL-4, IL-13, IL-31), baricitinib reduced epidermal keratinocyte pSTAT3 expression, and increased the expression of filaggrin, a protein that plays a role in skin barrier function and in the pathogenesis of atopic dermatitis.

Vaccine study
The influence of baricitinib on the humoral response to non-live vaccines was evaluated in 106 rheumatoid arthritis 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 % (95 % CI: 58.4 %, 76.2 %) of the patients. In 43.1 % (95 % CI: 34 %, 52.8 %) of the patients, a satisfactory IgG immune response to tetanus vaccination was achieved.

Clinical efficacy

Rheumatoid arthritis
The efficacy and safety of baricitinib once daily were assessed in 4 Phase III randomised, double-blind, multicentre studies in adult patients with moderate to severe active rheumatoid arthritis diagnosed according to the ACR/EULAR 2010 criteria (Table 3). 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.
Table 3. Clinical trial summary

<table>
<thead>
<tr>
<th>Study name (Duration)</th>
<th>Population (Number)</th>
<th>Treatment arms</th>
<th>Summary of key outcome measures</th>
</tr>
</thead>
</table>
| RA-BEGIN (52 weeks)   | MTX-naïve¹ (584)    | • Baricitinib 4 mg QD  
• Baricitinib 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-IR² (1305)      | • Baricitinib 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-IR³ (684)    | • Baricitinib 4 mg QD  
• Baricitinib 2 mg QD  
• Placebo  
On background cDMARDs⁵ 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-IR⁴ (527)       | • Baricitinib 4 mg QD  
• Baricitinib 2 mg QD  
• Placebo  
On background cDMARDs⁵ | • 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 ¹Patients who had received less than 3 doses of Methotrexate (MTX); naïve to other conventional or biologic DMARDs ²Patients who had an inadequate response to MTX (+/- other cDMARDs); biologic-naïve ³Patients who had an inadequate response or were intolerant to ≥ 1 cDMARDs; biologic- naïve ⁴Patients who had an inadequate response or were intolerant to ≥ 1 bDMARDs; including at least one TNF inhibitor ⁵Most common concomitant cDMARDs included MTX, hydroxychloroquine, leflunomide and sulfasalazine

Clinical response
In all studies, patients treated with baricitinib 4 mg once daily had statistically significantly higher ACR20, ACR50 and ACR70 response at 12 weeks compared to placebo, MTX or adalimumab (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 baricitinib 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,MTX or adalimumab.

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 baricitinib 4 mg compared to placebo or MTX achieved remission (SDAI ≤ 3.3 and CDAI ≤ 2.8) or low disease activity or
Greater rates of remission compared to placebo were observed as early as week 4. Remission and low disease activity rates were maintained for at least 2 years.

**Table 4: Response, remission and physical function**

<table>
<thead>
<tr>
<th>Study</th>
<th>RA-BEGIN MTX-naïve patients</th>
<th>RA-BEAM MTX-IR patients</th>
<th>RA-BUILD cDMARD-IR patients</th>
<th>RA-BEACON TNF-IR patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>MTX 4 mg</td>
<td>BARI 4 mg</td>
<td>BARI 4 mg + MTX</td>
<td>PBO 40 mg Q2W</td>
</tr>
<tr>
<td>N</td>
<td>210</td>
<td>159</td>
<td>215</td>
<td>488</td>
</tr>
<tr>
<td>ACR20:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>59%</td>
<td>79%</td>
<td>77%</td>
<td>40%</td>
</tr>
<tr>
<td>Week 24</td>
<td>62%</td>
<td>77%</td>
<td>78%</td>
<td>37%</td>
</tr>
<tr>
<td>Week 52</td>
<td>56%</td>
<td>73%</td>
<td>73%</td>
<td>71%†</td>
</tr>
<tr>
<td>ACR50:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>33%</td>
<td>55%</td>
<td>60%</td>
<td>17%</td>
</tr>
<tr>
<td>Week 24</td>
<td>43%</td>
<td>60%</td>
<td>63%</td>
<td>19%</td>
</tr>
<tr>
<td>Week 52</td>
<td>38%</td>
<td>57%</td>
<td>62%</td>
<td>56%†</td>
</tr>
<tr>
<td>ACR70:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>16%</td>
<td>31%</td>
<td>34%</td>
<td>5%</td>
</tr>
<tr>
<td>Week 24</td>
<td>21%</td>
<td>42%</td>
<td>40%</td>
<td>8%</td>
</tr>
<tr>
<td>Week 52</td>
<td>25%</td>
<td>42%</td>
<td>46%</td>
<td>37%</td>
</tr>
<tr>
<td>DAS28-hsCRP ≤ 3.2:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>30%</td>
<td>47%</td>
<td>56%</td>
<td>14%</td>
</tr>
<tr>
<td>Week 24</td>
<td>38%</td>
<td>57%</td>
<td>60%</td>
<td>19%</td>
</tr>
<tr>
<td>Week 52</td>
<td>38%</td>
<td>57%</td>
<td>63%</td>
<td>56%†</td>
</tr>
<tr>
<td>SDAI ≤ 3.3:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>6%</td>
<td>14%</td>
<td>20%</td>
<td>2%</td>
</tr>
<tr>
<td>Week 24</td>
<td>10%</td>
<td>22%</td>
<td>23%</td>
<td>3%</td>
</tr>
<tr>
<td>Week 52</td>
<td>13%</td>
<td>25%</td>
<td>30%</td>
<td>23%</td>
</tr>
<tr>
<td>CDAI ≤ 2.8:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>7%</td>
<td>14%</td>
<td>19%</td>
<td>2%</td>
</tr>
<tr>
<td>Week 24</td>
<td>11%</td>
<td>21%</td>
<td>22%</td>
<td>4%</td>
</tr>
<tr>
<td>Week 52</td>
<td>16%</td>
<td>25%</td>
<td>28%</td>
<td>22%</td>
</tr>
<tr>
<td>HAQ-DI Minimum Clinically Important Difference (decrease in HAQ-DI score of ≥ 0.30):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>60%</td>
<td>81%</td>
<td>77%</td>
<td>46%</td>
</tr>
<tr>
<td>Week 24</td>
<td>66%</td>
<td>77%</td>
<td>74%</td>
<td>37%</td>
</tr>
<tr>
<td>Week 52</td>
<td>53%</td>
<td>65%</td>
<td>67%</td>
<td>61%</td>
</tr>
</tbody>
</table>

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; BARI = baricitinib; MTX = methotrexate; 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 baricitinib 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 baricitinib 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 baricitinib 4 mg compared to placebo at weeks 24 and 52.

Table 5. Radiographic changes

<table>
<thead>
<tr>
<th>Study</th>
<th>RA-BEGIN MTX-naïve patients</th>
<th>RA-BEAM MTX-IR patients</th>
<th>RA-BUILD cDMARD-IR patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>MTX</td>
<td>BARI4 mg</td>
<td>BARI4 mg + MTX</td>
</tr>
<tr>
<td><strong>Modified Total Sharp Score, mean change from baseline:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>0.61</td>
<td>0.39</td>
<td>0.29*</td>
</tr>
<tr>
<td>Week 52</td>
<td>1.02</td>
<td>0.80</td>
<td>0.40**</td>
</tr>
<tr>
<td><strong>Proportion of patients with no radiographic progressiona:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>68 %</td>
<td>76 %</td>
<td>81 %**</td>
</tr>
<tr>
<td>Week 52</td>
<td>66 %</td>
<td>69 %</td>
<td>80 %**</td>
</tr>
</tbody>
</table>

Abbreviations: ADA = adalimumab; BARI = baricitinib; MTX = methotrexate; PBO = Placebo

* Placebo data at week 52 derived using linear extrapolation

** 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 baricitinib 4 mg, alone or in combination with cDMARDs, resulted in a significant improvement in physical function (HAQ-DI) and pain (0-100 visual analogue scale) compared to all comparators (placebo, MTX, adalimumab). Improvements were 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 baricitinib 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.

In all studies, baricitinib-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).

Baricitinib 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 baricitinib 4 mg compared to placebo at week 24 but not for baricitinib 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 baricitinib 4 mg once daily were re-randomised 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.

**Atopic dermatitis**

The efficacy and safety of baricitinib as monotherapy or in combination with topical corticosteroids (TCS) were assessed in 3 Phase III randomised, double-blind, placebo-controlled, 16 week studies (BREEZE-AD1, -AD2, and -AD7). The studies included 1 568 patients with moderate to severe atopic dermatitis defined by Investigator's Global Assessment (IGA) score ≥ 3, an Eczema Area and Severity Index (EASI) score ≥ 16, and a body surface area (BSA) involvement of ≥ 10 %. Eligible patients were over 18 years of age and had previous inadequate response or were intolerant to topical medication. Patients were permitted to receive rescue treatment (which included topical or systemic therapy), at which time they were considered non-responders. At baseline of study BREEZE-AD7, all patients were on concomitant topical corticosteroids therapy and patients were permitted to use topical calcineurin inhibitors. All patients who completed these studies were eligible to enrol in a long term extension study (BREEZE AD-3) for up to 2 years of continued treatment.

The Phase III randomised, double-blind, placebo-controlled BREEZE-AD4 study evaluated the efficacy of baricitinib in combination with topical corticosteroids over 52 weeks in 463 patients with moderate to severe atopic dermatitis with failure, intolerance, or contraindication to oral ciclosporin treatment.

**Baseline characteristics**

In the placebo-controlled Phase III studies (BREEZE-AD1, -AD2, -AD7, and -AD4), across all treatment groups, 37 % were female, 64 % were Caucasian, 31 % were Asian and 0.6 % were Black, and the mean age was 35.6 years. In these studies, 42 % to 51 % of patients had a baseline IGA of 4 (severe atopic dermatitis), and 54 % to 79 % of patients had received prior systemic treatment for atopic dermatitis. The baseline mean EASI score ranged from 29.6 to 33.5, the baseline weekly averaged Itch Numerical Rating Scale (NRS) ranged from 6.5 to 7.1, the baseline mean Dermatology Life Quality Index (DLQI) ranged from 13.6 to 14.9, and the baseline mean Hospital Anxiety and Depression Scale (HADS) Total score ranged from 10.9 to 12.1.

**Clinical response**

16-week monotherapy (BREEZE-AD1, -AD2) and TCS combination (BREEZE-AD7) studies

A significantly larger proportion of patients randomised to baricitinib 4 mg achieved an IGA 0 or 1 response (primary outcome), EASI75, or an improvement of ≥ 4 points on the Itch NRS compared to placebo at week 16 (Table 6). Figure 1 shows the mean percent change from baseline in EASI up to week 16.

A significantly greater proportion of patients randomised to baricitinib 4 mg achieved a ≥ 4-point improvement in the Itch NRS compared to placebo (within the first week of treatment for BREEZE-AD1 and AD2, and as early as week 2 for BREEZE-AD7; p < 0.002).

Treatment effects in subgroups (weight, age, gender, race, disease severity, and previous treatment, including immunosuppressants) were consistent with the results in the overall study population.
Table 6. Efficacy of baricitinib at week 16 (FAS*)

<table>
<thead>
<tr>
<th>Study</th>
<th>Monotherapy</th>
<th>TCS Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BREEZE-AD1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BREEZE-AD2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BREEZE-AD7</td>
<td></td>
</tr>
<tr>
<td>Treatment Group</td>
<td>PBO</td>
<td>PBO + TCS</td>
</tr>
<tr>
<td></td>
<td>BARI 2 mg</td>
<td>BARI 2 mg + TCS</td>
</tr>
<tr>
<td></td>
<td>BARI 4 mg</td>
<td>BARI 4 mg + TCS</td>
</tr>
<tr>
<td>N</td>
<td>249</td>
<td>109</td>
</tr>
<tr>
<td>IGA 0 or 1, % responders&lt;sup&gt;bc&lt;/sup&gt;</td>
<td>4.8</td>
<td>11.4**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.5</td>
</tr>
<tr>
<td>EASI-75, % responders&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.8</td>
<td>18.7**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.1</td>
</tr>
<tr>
<td>Itch NRS (≥ 4 point improvement), % responders&lt;sup&gt;cd&lt;/sup&gt;</td>
<td>7.2</td>
<td>12.0</td>
</tr>
</tbody>
</table>

BARI = Baricitinib; PBO = Placebo
* statistically significant vs placebo without adjustment for multiplicity; ** statistically significant vs placebo with adjustment for multiplicity.
<sup>a</sup> Full analysis set (FAS) including all randomised patients.
<sup>b</sup> Responder was defined as a patient with IGA 0 or 1 (“clear” or “almost clear”) with a reduction of ≥ 2 points on 0-4 IGA scale.
<sup>c</sup> Non-Responder Imputation: Patients who received rescue treatment or with missing data were considered as non-responders.
<sup>d</sup> Results shown in subset of patients eligible for assessment (patients with itch NRS ≥ 4 at baseline).

Figure 1. Mean percent change from baseline in EASI (FAS)*

LS = Least squares; * statistically significant vs placebo without adjustment for multiplicity; ** statistically significant vs placebo with adjustment for multiplicity.
<sup>a</sup> Full analysis set (FAS) including all patients randomised. Data collected after rescue therapy or after permanent medicinal product discontinuation were considered missing. LS means are from Mixed Model with Repeated Measures (MMRM) analyses.

Maintenance of response

To evaluate maintenance of response, 1 373 subjects treated with baricitinib for 16 weeks in BREEZE-AD1 (N = 541), BREEZE-AD2 (N = 540) and BREEZE-AD7 (N = 292) were eligible to enrol in a long term extension study BREEZE-AD3. Data are available up to 68 weeks of cumulative treatment for patients from BREEZE-AD1 and BREEZE-AD2, and up to 32 weeks of cumulative
treatment for patients from BREEZE-AD7. Continued response was observed in patients with at least some response (IGA 0, 1 or 2) after initiating baricitinib.

Quality of life/patient-reported outcomes in atopic dermatitis
In both monotherapy studies (BREEZE-AD1 and BREEZE-AD2) and in the concomitant TCS study (BREEZE-AD7), baricitinib 4 mg significantly improved patient-reported outcomes, including itch NRS, sleep (ADSS), skin pain (skin pain NRS), quality of life (DLQI) and symptoms of anxiety and depression (HADS) that were uncorrected for multiplicity, at 16 weeks compared to placebo (See Table 7).

Table 7. Quality of life/patient-reported outcomes results of baricitinib monotherapy and baricitinib in combination with TCS at week 16 (FAS)*

<table>
<thead>
<tr>
<th>Study</th>
<th>Monotherapy</th>
<th>TCS Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BREEZE-AD1</td>
<td>BREEZE-AD2</td>
</tr>
<tr>
<td>Treatment group</td>
<td>PBO 2 mg</td>
<td>BARI 4 mg</td>
</tr>
<tr>
<td>N</td>
<td>249</td>
<td>123</td>
</tr>
<tr>
<td>ADSS Item 2 ≥ 2-point improvement, % responders c,d</td>
<td>12.8</td>
<td>11.4</td>
</tr>
<tr>
<td>Change in Skin Pain NRS, mean(SE)b</td>
<td>-0.84</td>
<td>-1.58</td>
</tr>
<tr>
<td>Change in DLQI, mean(SE)b</td>
<td>-2.46</td>
<td>-4.30*</td>
</tr>
<tr>
<td>Change in HADS, mean(SE)b</td>
<td>-1.22</td>
<td>-3.22*</td>
</tr>
</tbody>
</table>

BARI = Baricitinib; PBO = Placebo
* statistically significant vs placebo without adjustment for multiplicity; ** statistically significant vs placebo with adjustment for multiplicity.

a Full analysis set (FAS) including all randomised patients.
b Results shown are LS mean change from baseline (SE). Data collected after rescue therapy or after permanent medicinal product discontinuation were considered missing. LS means are from Mixed Model with Repeated Measures (MMRM) analyses.
c ADSS Item 2: Number of night time awakenings due to itch.
d Nonresponder imputation: patients who received rescue treatment or with missing data were considered as nonresponders. Results shown in subset of patients eligible for assessment (patients with ADSS Item 2 ≥ 2 at baseline).

Clinical response in patients with experience with or a contra-indication to ciclosporin treatment (BREEZE-AD4 study)
A total of 463 patients were enrolled, who had either failed (n = 173), or had an intolerance (n = 75), or contraindication (n = 126) to oral ciclosporin. The primary endpoint was the proportion of patients achieving EASI-75 at week 16. The primary and some of the most important secondary endpoints at week 16 are summarised in Table 8.
### Table 8: Efficacy of baricitinib in combination with TCS<sup>a</sup> at week 16 in BREEZE-AD4 (FAS)<sup>b</sup>

<table>
<thead>
<tr>
<th>Study</th>
<th>BREEZE- AD4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>N</td>
<td>93</td>
</tr>
<tr>
<td>EASI-75, % responders&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17.2</td>
</tr>
<tr>
<td>IGA 0 or 1, % responders&lt;sup&gt;c, e&lt;/sup&gt;</td>
<td>9.7</td>
</tr>
<tr>
<td>Itch NRS (≥ 4 point improvement), % responders&lt;sup&gt;c, f&lt;/sup&gt;</td>
<td>8.2</td>
</tr>
<tr>
<td>Change in DLQI mean (SE)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-4.95 (0.752)</td>
</tr>
</tbody>
</table>

BARI = Baricitinib; PBO = Placebo
* statistically significant vs placebo without adjustment for multiplicity; ** statistically significant vs placebo with adjustment for multiplicity.
<sup>a</sup> All patients were on concomitant topical corticosteroids therapy and patients were permitted to use topical calcineurin inhibitors.
<sup>b</sup> Full analysis set (FAS) includes all randomised patients.
<sup>c</sup> Non-Responder Imputation: Patients who received rescue treatment or with missing data were considered as non-responders.
<sup>d</sup> Data collected after rescue therapy or after permanent medicinal product discontinuation were considered missing. LS means are from Mixed Model with Repeated Measures (MMRM) analyses.
<sup>e</sup> Responder was defined as a patient with IGA 0 or 1 (“clear” or “almost clear”) with a reduction of ≥ 2 points on 0-4 IGA scale.
<sup>f</sup> Results shown in subset of patients eligible for assessment (patients with itch NRS ≥ 4 at baseline).

**Paediatric population**

The European Medicines Agency has deferred the obligation to submit the results of studies with baricitinib in one or more subsets of the paediatric population in chronic idiopathic arthritis and atopic dermatitis (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 \( t_{\text{max}} \) 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 \( C_{\text{max}} \) by up to 18 % and delayed \( t_{\text{max}} \) 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 concentrations.

**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\(_{\text{max}}\) and AUC at steady state are 1.4- and 2.0-fold higher, respectively, in subjects with rheumatoid arthritis compared to healthy subjects.

Mean apparent clearance (CL/F) and half-life in patients with atopic dermatitis was 11.2 L/hr (CV = 33.0%) and 12.9 hrs (CV = 36.0%), respectively. C\(_{\text{max}}\) and AUC at steady state in patients with atopic dermatitis are 0.8-fold those seen in rheumatoid arthritis.

**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\(_{\text{max}}\) 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\(_{\text{max}}\) 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\(_{\text{max}}\)) 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

- iron oxide red (E172)
- lecithin (soya) (E322)
- macrogol
- poly (vinyl alcohol)
- talc
- titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.
6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyvinylchloride/polyethylene/polychlorotrifluoroethylene - aluminium blisters in cartons of 14, 28, 35, 56, 84 or 98 film-coated tablets.

Polyvinylchloride/aluminium/oriented polyamide - aluminium perforated unit dose blisters in cartons of 28 x 1 or 84 x 1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528BJ Utrecht, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

Olumiant 2 mg film-coated tablets

EU/1/16/1170/001
EU/1/16/1170/002
EU/1/16/1170/003
EU/1/16/1170/004
EU/1/16/1170/005
EU/1/16/1170/006
EU/1/16/1170/007
EU/1/16/1170/008

Olumiant 4 mg film-coated tablets

EU/1/16/1170/009
EU/1/16/1170/010
EU/1/16/1170/011
EU/1/16/1170/012
EU/1/16/1170/013
EU/1/16/1170/014
EU/1/16/1170/015
EU/1/16/1170/016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 February 2017
Date of latest renewal:
10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic safety update reports (PSURs)

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- Additional risk minimisation measures

Prior to launch of baricitinib in each Member State, the MAH must agree about the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The main objectives of the programme are to make the prescribers aware of the risks associated with the product’s use, and to highlight specific risk minimisation measures to be performed before and during the treatment with baricitinib.
The MAH shall ensure that, in each Member State where baricitinib is marketed, all healthcare professionals who are expected to prescribe baricitinib are provided with the physician educational material, which should contain:

- The Summary of Product Characteristics
- The Package Leaflet including the Patient Alert Card
- The guide for healthcare professionals to support counselling of the patient
- Additional Patient Alert Cards

**The guide for healthcare professionals** shall contain the following key elements:

- That baricitinib increases the potential risk of infections. Patients should be instructed to seek immediate medical attention, if signs or symptoms suggesting infection appear.
- That baricitinib use should be stopped in case of herpes zoster or any other infection that doesn’t respond to standard treatment until the event resolves. Patients should not be immunised using live attenuated vaccines shortly before or during treatment with baricitinib.
- Prescribers should screen the patients for viral hepatitis before commencing baricitinib treatment. Active tuberculosis should also be ruled out.
- That baricitinib use is associated with hyperlipidaemia; prescribers should monitor the patient’s lipid parameters and manage the hyperlipidaemia, if detected.
- That cases 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. Patients should be instructed to seek immediate medical attention if signs or symptoms of DVT/PE appear.
- That baricitinib is contraindicated in pregnancy as pre-clinical data showed reduced foetal growth and malformations. Physicians should advise women of child bearing potential to use contraception during treatment and for a week after its ending. If a planned pregnancy is considered, baricitinib treatment should be stopped.
- The purpose and use of the Patient Alert Card.

**The patient alert card** shall contain the following key messages:

- That treatment with baricitinib may increase the risk of infections, and viral reactivation.
- Signs or symptoms of infections including general symptoms, and specifically tuberculosis and herpes zoster signs and symptoms; and a warning for the patients to seek immediate medical attention if signs or symptoms suggesting infection appear.
- That baricitinib should not be taken while pregnant and that women should inform their doctor should they become (or wish to become) pregnant.
- That the patient may need to have their cholesterol level checked during treatment.
- That baricitinib may cause a blood clot in the leg that may travel to the lungs; a description of signs and symptoms is provided, along with a warning for the patients to seek immediate medical attention if signs or symptoms suggesting a blood clot appear.
- Contact details of the prescriber.
- That the Patient Alert Card should be carried by the patient at any time and to share it with other healthcare professionals involved in their treatment.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTONS FOR 2 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Olumiant 2 mg film-coated tablets
baricitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2 mg baricitinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
35 film-coated tablets
56 film-coated tablets
84 film-coated tablets
98 film-coated tablets
28 x 1 film-coated tablets
84 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

QR code to be included+ www.olumiant.eu

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528BJ Utrecht, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

<table>
<thead>
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<th>Number</th>
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13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Olumiant 2 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN
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<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
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<tr>
<td>CALENDAR BLISTERS NON-PERFORATED FOR 2 MG FILM-COATED TABLETS</td>
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1. **NAME OF THE MEDICINAL PRODUCT**

   Olumiant 2 mg tablets  
   baricitinib

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

   Lilly

3. **EXPIRY DATE**

   EXP

4. **BATCH NUMBER**

   Lot

5. **OTHER**

   Mon.  
   Tue.  
   Wed.  
   Thu.  
   Fri.  
   Sat.  
   Sun.
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

**BLISTERS PERFORATED UNIT DOSE FOR 2 MG FILM-COATED TABLETS**

#### 1. NAME OF THE MEDICINAL PRODUCT

Olumiant 2 mg tablets  
baricitinib

#### 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

#### 3. EXPIRY DATE

EXP

#### 4. BATCH NUMBER

Lot

#### 5. OTHER
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTONS FOR 4 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Olumiant 4 mg film-coated tablets
baricitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 4 mg baricitinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
35 film-coated tablets
56 film-coated tablets
84 film-coated tablets
98 film-coated tablets
28 x 1 film-coated tablets
84 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

QR code to be included+ www.olumiant.eu

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528BJ Utrecht, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

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13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Olumiant 4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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SN
NN
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<td>Sat.</td>
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<td>Sun.</td>
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## MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

**BLISTERS PERFORATED UNIT DOSE FOR 4 MG FILM-COATED TABLETS**

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<th>5. OTHER</th>
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</table>
B. PACKAGE LEAFLET
Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Olumiant is and what it is used for
2. What you need to know before you take Olumiant
3. How to take Olumiant
4. Possible side effects
5. How to store Olumiant
6. Contents of the pack and other information

1. What Olumiant is and what it is used for

Olumiant contains the active substance baricitinib. It belongs to a group of medicines called Janus kinase inhibitors, which help to reduce inflammation.

Rheumatoid arthritis
Olumiant is used to treat adults with moderate to severe rheumatoid arthritis, an inflammatory disease of the joints, if previous therapy did not work well enough or was not tolerated. Olumiant can be used alone or together with some other medicines, such as methotrexate.

Olumiant works by reducing the activity of an enzyme in the body called ‘Janus kinase’, which is involved in inflammation. By reducing the activity of this enzyme, Olumiant helps to reduce pain, stiffness and swelling in your joints, tiredness, and helps to slow damage to the bone and cartilage in the joints. These effects can help you to do normal daily activities and so improve the health-related quality of life for patients with rheumatoid arthritis.

Atopic dermatitis
Olumiant is used to treat adults with moderate to severe atopic dermatitis, also known as atopic eczema. Olumiant may be used with eczema medicines that you apply to the skin or it may be used on its own.

Olumiant works by reducing the activity of an enzyme in the body called ‘Janus kinase’, which is involved in inflammation. By reducing the activity of this enzyme, Olumiant helps to improve the condition of your skin and reduce itching. In addition, Olumiant helps improve your sleep disturbance (due to itch) and overall quality of life. Olumiant has also been shown to improve symptoms of skin pain, anxiety, and depression associated with atopic dermatitis.
2. What you need to know before you take Olumiant

Do not take Olumiant
- if you are allergic to baricitinib or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant or think you may be pregnant.

Warnings and precautions
Talk to your doctor or pharmacist before and during treatment with Olumiant if you:
- have an infection, or if you often get infections. Tell your doctor if you get symptoms such as fever, wounds, feeling more tired than usual or dental problems as these can be signs of infection. Olumiant can reduce your body’s ability to fight infections and may make an existing infection worse or increase the chance of you getting a new infection
- have, or have previously had, tuberculosis. You may need tests to check for tuberculosis before you are given Olumiant. Tell your doctor if you get persistent cough, fever, night sweats and weight loss during Olumiant treatment as these can be signs of tuberculosis
- have had a herpes infection (shingles), because Olumiant may allow it to come back. Tell your doctor if you get painful skin rash with blisters during Olumiant treatment as these can be signs of shingles
- have, or have previously had, hepatitis B or C
- are due to have a vaccine. You should not be given certain (live) vaccines while using Olumiant
- have cancer, because your doctor will have to decide if you can still be given Olumiant
- have poor liver function
- have previously had blood clots in the veins of your legs (deep vein thrombosis) or lungs (pulmonary embolism). Tell your doctor if you get a painful swollen leg, chest pain, or shortness of breath as these can be signs of blood clots in the veins
- have had diverticulitis (a type of inflammation of the large intestine) or ulcers in stomach or intestines (see section 4)

If you notice any of the following serious side effects, you need to tell a doctor straight away:
- chest tightness
- wheezing
- severe dizziness or light-headedness
- swelling of the lips, tongue or throat
- hives (itching or skin rash)
- severe abdominal pain especially accompanied with fever, nausea and vomiting.

You may need blood tests before you start Olumiant, or while you are taking it, to check if you have a low red blood cell count (anaemia), low white blood cell count (neutropaenia or lymphopaenia), high blood fat (cholesterol) or high levels of liver enzymes, to ensure that treatment with Olumiant is not causing problems.

Children and adolescents
Do not give this medicine to children and adolescents under 18 years old because there is no information on use in this age group.

Other medicines and Olumiant
Tell your doctor or pharmacist if you are taking, have recently taken, or might take, any other medicines.

In particular, tell your doctor or pharmacist before taking Olumiant if you are taking any other medicine such as:
- probenecid (for gout), since this medicine may increase the levels of Olumiant in your blood. If you are taking probenecid, the recommended dose of Olumiant is 2 mg once a day
- injectable anti-rheumatic medicine
- injectable medicines that depress the immune system, including so called targeted biologic (antibody) therapies
medicines which are used to control the body’s immune response, such as azathioprine, tacrolimus or ciclosporin
- other medicines belonging to the group of Janus kinase inhibitors
- medicines that may increase your risk of diverticulitis such as a non-steroidal anti-inflammatory medicines (usually used to treat painful and/or inflammatory conditions of muscle or joints) and/or opioids (used to treat severe pain), and/or corticosteroids (usually used to treat inflammatory conditions) (see section 4)

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

You should use an effective method of contraception to avoid becoming pregnant during treatment with Olumiant and for at least one week after the last Olumiant treatment. You must tell your doctor if you become pregnant as Olumiant should not be used during pregnancy.

You should not use Olumiant while breast-feeding as it is not known if this medicine passes into milk. You and your doctor should decide if you will breast-feed or use Olumiant. You should not do both.

**Driving and using machines**
Olumiant has no effect on the ability to drive and use machines.

**Olumiant contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

### 3. How to take Olumiant

Treatment should be started by a doctor experienced in the diagnosis and treatment of your condition. Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

**Rheumatoid arthritis and atopic dermatitis**
The recommended dose is 4 mg once a day. Your doctor may give you a lower dose of 2 mg once a day, particularly if you are over 75 years old or if you have an increased risk of infections. If the medicine is working well, your doctor may decide the dose can be reduced.

If you have reduced kidney function, the recommended dose of Olumiant is 2 mg once a day.

Olumiant is for oral use. You should swallow your tablet with a drink of water. You can take the tablets either with or without food. To help you remember to take Olumiant, you may find it easier to take it at the same time every day.

**If you take more Olumiant than you should**
If you take more Olumiant than you should, contact your doctor. You may get some of the side effects described in section 4.

**If you forget to take Olumiant**
- If you miss a dose, take it as soon as you remember.
- If you forget your dose for an entire day, just skip the missed dose and take only a single dose as usual the following day.
- Do not take a double dose to make up for a forgotten tablet.

**If you stop taking Olumiant**
Do not stop taking Olumiant unless your doctor tells you to stop taking it.
4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

**Infection such as shingles and pneumonia**, which may affect up to 1 in 10 people:
Tell your doctor or seek medical help immediately if you get the following symptoms, which may be signs of:
- shingles (herpes zoster): painful skin rash with blisters and fever (this was very rare in atopic dermatitis)
- pneumonia: persistent cough, fever, shortness of breath, and tiredness (this was uncommon in atopic dermatitis)

Serious pneumonia and serious herpes zoster were uncommon.

Other side effects

**Very common** (may affect more than 1 in 10 people)
- throat and nose infections
- high levels of blood fat (cholesterol) shown by blood test

**Common** (may affect up to 1 in 10 people)
- cold sores (herpes simplex)
- infection causing a sick stomach or diarrhoea (gastroenteritis)
- urinary infection
- high number of platelets (cells involved in blood clotting), shown by blood test (this was uncommon in atopic dermatitis)
- headache
- feeling sick in the stomach (nausea; this was uncommon in atopic dermatitis)
- stomach pain
- high levels of liver enzymes, shown by blood test (this was uncommon in atopic dermatitis)
- rash
- acne (this was uncommon in rheumatoid arthritis)
- increase in an enzyme called creatine kinase, shown by a blood test (this was uncommon in rheumatoid arthritis)

**Uncommon** (may affect up to 1 in 100 people)
- low number of white bloods cells (neutrophils), shown by blood test
- high levels of blood fat (triglycerides), shown by blood test
- high levels of liver enzymes, shown by blood test
- weight gain
- swelling of the face
- urticaria
- blood clots in the blood vessels of the lungs
- blood clot in the veins of the legs or pelvis, called a deep vein thrombosis (DVT)
- diverticulitis (painful inflammation of small pockets in the lining of your intestine)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.
5. How to store Olumiant

Keep this medicine out of the sight and reach of children.

This medicine does not require any special storage conditions.

Do not use this medicine after the expiry date which is stated on the blister and carton after ‘EXP’. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Olumiant contains
- The active substance is baricitinib. Each tablet contains 2 or 4 milligrams of baricitinib.

- The other ingredients are: microcrystalline cellulose, croscarmellose sodium, (see section 2 “Olumiant contains sodium”) magnesium stearate, mannitol, iron oxide red (E172), lecithin (soya) (E322), macrogol, poly (vinyl alcohol), talc and titanium dioxide (E171).

What Olumiant looks like and contents of the pack
Olumiant 2 mg film-coated tablets are light pink, 9 x 7.5 mm oblong tablets, with “Lilly” on one side and “2” on the other.

Olumiant 4 mg film-coated tablets are medium pink, 8.5 mm round tablets, with “Lilly” on one side and “4” on the other.

The tablets are rounded and have hollow sides to help you pick them up.

Olumiant 2 mg and 4 mg are available in blister packs of 14, 28, 35, 56, 84 and 98 tablets in calendar blisters and 28 x 1 and 84 x 1 tablets in perforated unit dose blisters. Not all the pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Belgique/België/Belgien
Eli Lilly Benelux S.A./N.V.
Tél/Tel: + 32-(0)2 548 84 84

Lietuva
Eli Lilly Lietuva
Tel. +370 (5) 2649600

България
TP "Ели Лили Нederland" Б.В. - България
tel. + 359 2 491 41 40

Luxembourg/Luxemburg
Eli Lilly Benelux S.A./N.V.
Tél/Tel: + 32-(0)2 548 84 84

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ELI LILLY ČR, s.r.o.
Tel: + 420 234 664 111

Magyarország
Lilly Hungária Kft.
Tel: + 36 1 328 5100
**Danmark**  
Eli Lilly Danmark A/S  
Tel: +45 45 26 60 00

**Deutschland**  
Lilly Deutschland GmbH  
Tel. + 49-(0) 6172 273 2222

**Eesti**  
Eli Lilly Nederland B.V.  
Tel: +372 6 817 280

**Ελλάδα**  
ΦΑΡΜΑΣΕΡΒ-ΛΙΛΛΥ Α.Ε.Β.Ε.  
Τηλ.: +30 210 629 4600

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Lilly S.A.  
Tel: + 34-91 663 50 00

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Lilly France  
Tel: +33-(0) 1 55 49 34 34

**Hrvatska**  
Eli Lilly Hrvatska d.o.o.  
Tel: +385 1 2350 999

**Irland**  
Eli Lilly and Company (Ireland) Limited  
Tel: + 353-(0) 1 661 4377

**Ísland**  
Icepharma hf.  
Sími + 354 540 8000

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Eli Lilly Italia S.p.A.  
Tel: + 39- 055 42571

**Κύπρος**  
Phadisco Ltd  
Τηλ: +357 22 715000

**Latvija**  
Eli Lilly (Suisse) S.A Pārstāvniecība Latvijā  
Tel: +371 67364000

**Malta**  
Charles de Giorgio Ltd.  
Tel: + 356 25600 500

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Eli Lilly Nederland B.V.  
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**Norge**  
Eli Lilly Norge A.S.  
Tel: + 47 22 88 18 00

**Österreich**  
Eli Lilly Ges.m.b.H.  
Tel: + 43-(0) 1 711 780

**Polska**  
Eli Lilly Polska Sp. z o.o.  
Tel: +48 22 440 33 00

**Portugal**  
Lilly Portugal Produtos Farmacêuticos, Lda  
Tel: + 351-21-4126600

**România**  
Eli Lilly România S.R.L.  
Tel: + 40 21 4023000

**Slovenija**  
Eli Lilly farmacevtska družba, d.o.o.  
Tel: +386 (0)1 580 00 10

**Slovenská republika**  
Eli Lilly Slovakia s.r.o.  
Tel: + 421 220 663 111

**Suomi/Finland**  
Oy Eli Lilly Finland Ab  
Puh/Tel: + 358-(0) 9 85 45 250

**Sverige**  
Eli Lilly Sweden AB  
Tel: + 46-(0) 8 7378800

**United Kingdom (Northern Ireland)**  
Eli Lilly and Company (Ireland) Limited  
Tel: + 353-(0) 1 661 4377

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:  

QR code to be included + [www.olumiant.eu](http://www.olumiant.eu)
Information for Patients about OLUMIANT (baricitinib)
This document contains important information you should be aware of before and during treatment with Olumiant.

Keep this information with you and share it with other healthcare professionals involved in your medical care or treatment.

Your name: _______________________________________

Doctor’s name (who prescribed Olumiant): ________________________________

Doctor’s phone number: ______________________________________

<table>
<thead>
<tr>
<th>Pregnancy:</th>
<th></th>
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<tbody>
<tr>
<td>• Do not take Olumiant if you are pregnant or suspect you may be pregnant.</td>
<td></td>
</tr>
<tr>
<td>• Use effective contraception while taking Olumiant (and for 1 week after, if you stop treatment).</td>
<td></td>
</tr>
<tr>
<td>• Tell your doctor immediately if you become (or wish to become) pregnant.</td>
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<thead>
<tr>
<th>Infections:</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Olumiant may make an existing infection worse or increase the chance of you getting a new infection or increase the chance of viral reactivation. Inform your doctor immediately if you get symptoms of infection, such as:</td>
<td></td>
</tr>
<tr>
<td>• Fever, wounds, feeling more tired than usual, or dental problems.</td>
<td></td>
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<tr>
<td>• A cough that won't go away, night sweats, and weight loss. These could be symptoms of tuberculosis (an infectious disease of the lungs).</td>
<td></td>
</tr>
<tr>
<td>• A painful skin rash with blisters. This could be a sign of a herpes zoster infection.</td>
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<tr>
<th>Blood fat:</th>
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</thead>
<tbody>
<tr>
<td>Your doctor may check for levels of fat in the blood, such as cholesterol, while you are taking Olumiant.</td>
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<tr>
<th>Blood clots:</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Olumiant may cause a condition in which a blood clot forms in your leg that may travel to your lungs. Inform your doctor immediately if you experience any of the following symptoms:</td>
<td></td>
</tr>
<tr>
<td>• Swelling or pain in one leg</td>
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<tr>
<td>• Warmth or redness in one leg</td>
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</tr>
<tr>
<td>• Shortness of breath which is unexpected</td>
<td></td>
</tr>
<tr>
<td>• Rapid breathing</td>
<td></td>
</tr>
<tr>
<td>• Chest pain</td>
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</table>