APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

UNAMITY 2 mg film-coated tablets

UNAMITY 4 mg film-coated tablets

WARNING: SERIOUS INFECTIONS, MALIGNANCY AND THROMBOSIS

Patients treated with UNAMITY are at risk of developing serious infections that may lead to hospitalization or death [see Special Warnings and precautions for use (4.4) and Undesirable effects (4.8)]. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt treatment with UNAMITY until the infection is controlled.

Reported infections include:

- **Active tuberculosis which may present with pulmonary or extra pulmonary disease. Patients should be tested for latent tuberculosis before initiating treatment with UNAMITY and during therapy. Treatment for latent infection should be considered prior to UNAMITY use.**
- **Invasive fungal infection, including candidiasis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with UNAMITY should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with UNAMITY including the possible development of tuberculosis in patients who tested negative for latent tuberculosis prior to initiating therapy [see Special Warnings and precautions for use (4.4)].

UNAMITY may cause activation of Hepatitis B or C infection. If HBV or HCV DNA is detected, a liver specialist should be consulted to determine if treatment interruption is warranted.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with UNAMITY [see Special Warnings and precautions for use (4.4)].

THROMBOSIS

Thrombosis, including deep venous thrombosis and pulmonary embolism, has been observed at an increased incidence in patients treated with UNAMITY compared to placebo. In addition, there were cases of arterial thrombosis. Many of these adverse events were serious and some resulted in death. Patients with symptoms of thrombosis should be promptly evaluated [see Special Warnings and precautions for use (4.4)].

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

UNAMITY 2 mg film-coated tablets: Each film-coated tablet contains 2 mg baricitinib.

UNAMITY 4 mg film-coated tablets: Each film-coated tablet contains 4 mg baricitinib.

Contains sugar: mannitol

Each 2 mg film-coated tablet contains 52, 00 mg of mannitol.

Each 4 mg film-coated tablet contains 50, 00 mg of mannitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated Tablet

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

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

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Rheumatoid Arthritis

UNAMITY 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.

UNAMITY 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).

Limitations of use:

Use of UNAMITY in combination with other Janus Kinase (JAK) inhibitors, biologic disease-modifying anti-rheumatic medicines (DMARDs), or with potent immunosuppressants such as azathioprine and ciclosporin, has not been studied, and is not recommended.

COVID-19

UNAMITY is indicated for the treatment of coronavirus disease 2019 (COVID-19) in hospitalised adult and paediatric patients aged 10 years and older who require supplemental oxygen (see section 5.1).

4.2. Posology and method of administration

Treatment should be initiated by doctors experienced in the diagnosis and treatment of conditions for which baricitinib is indicated.

The patient should keep the Patient Alert Card with them at all times (see Patient Information Leaflet).

Posology

Rheumatoid Arthritis

The recommended dose of UNAMITY is 4 mg once daily.

A dose of 2 mg once daily is appropriate for patients 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).

COVID-19

The recommended dose of UNAMITY in patients 10 years of age and older is 4 mg once daily. The recommended treatment duration of UNAMITY is 14 days or until hospital discharge, whichever occurs first.

UNAMITY may be used with or without corticosteroids and with or without remdesivir.

Venous Thromboembolism (VTE) prophylaxis is recommended unless contraindicated (see section 4.4 Special warnings and precautions for use).

Treatment initiation

Rheumatoid Arthritis: 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).

COVID-19: There is limited information on the use of UNAMITY in patients with ALC< 0,2 x 10^9 cells/L, ANC< 1 x 10^9 cells/L , or haemoglobin < 8 g/dL.

Special populations

Renal impairment

Rheumatoid arthritis: The recommended dose is 2 mg once daily in patients with creatinine clearance between 30 and 60 mL/min. UNAMITY is not recommended for use in patients with creatinine clearance < 30 mL/min (see sections 4.3 and 5.2).

COVID-19: The recommended dose is 2 mg once daily in patients with creatinine clearance between 30 and 60 ml/min. The recommended dose of UNAMITY in patients with estimated glomerular filtration rate (GFR) between 15 and 30 ml/min is 2 mg once every 48 hours. Baricitinib is not recommended for use in patients with estimated GFR of < 15 mL/min (see sections 4.3 and 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment.

Rheumatoid Arthritis: UNAMITY is not recommended for use in patients with severe hepatic impairment (see section 5.2).

COVID-19*:* UNAMITY has not been studied in patients with severe hepatic impairment. Patients with COVID-19 who require low-flow oxygen or non-invasive ventilation/high-flow oxygen suffer from a serious, potentially life-threatening condition. Baricitinib should therefore only be used in patients with severe hepatic impairment if the potential benefit outweighs the potential risk.

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

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

COVID-19*:* No dose adjustment of UNAMITY is required in patients ≥ 75 years. The clinical experience in patients ≥ 75 years is limited.

Paediatric population

Rheumatoid Arthritis: The safety and efficacy of UNAMITY in children and adolescents aged 0 to 18 years have not yet been established. No data are available.

COVID-19: The safety and efficacy of UNAMITY in children under the age of 10 years have not yet been established. No data are available.

Method of administration

Oral use.

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

Alternate administration for COVID-19

For patients who are unable to swallow whole tablets, alternate administration may be considered:

- oral dispersion
- gastrostomy tube (G tube)
- nasogastric tube (NG tube) or orogastric tube (OG)

Tablets may be dispersed whole or may be crushed for dispersion. If tablets are crushed, use proper control measures or personal protective equipment.

- Place tablets in a container with at least the minimum dispersion volume (see Table 1) of room temperature water and gently swirl to disperse.
- Administer immediately.
- Rinse the container with at least the minimum volume of room temperature water (see Table 1) and administer immediately.

Table 1: Dispersion and Rinse Volumes for Alternate Administration

Administration via	**Dispersion Volume**	**Container Rinse Volume**
Oral dispersion	10 mL (5 mL minimum)	10 mL (5 mL minimum)
G tube	15 mL (10 mL minimum)	15 mL (10 mL minimum)
NG tube	30 mL	15 mL

4.3. Contraindications

UNAMITY is contraindicated in:

- Patients with hypersensitivity to baricitinib or to any of the excipients listed in section 6.1.

- Use in patients with estimated glomerular filtration rate of < 30 ml/ min/ 1,73 m^2 for longer term use (as in Rheumatoid arthritis) and < 15 ml/min/1,73 m^2 for short term use (as in COVID-19) (see section 5.2).
- Active tuberculosis and other active infections (see boxed warning).
- Pregnancy and lactation (see section 4.6).

4.4. Special warnings and precautions for use

Infections

UNAMITY 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 UNAMITY monotherapy.

The risks and benefits of treatment with UNAMITY should be carefully considered prior to initiating therapy in patients with active, chronic or recurrent infections (see section 4.2). For the treatment of COVID-19, see section 4.4, “COVID-19”.

If an infection develops, the patient should be monitored carefully and UNAMITY therapy should be temporarily interrupted if the patient is not responding to standard therapy. UNAMITY treatment should not be resumed until the infection resolves.

Tuberculosis

Patients should be screened for tuberculosis (TB) before starting UNAMITY therapy.

UNAMITY should not be given to patients with active TB.

Anti-TB therapy should be considered prior to initiation of UNAMITY 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 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). For the treatment of COVID-19, see section 4.4; “COVID-19”.

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, UNAMITY 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 UNAMITY for rheumatoid arthritis. 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 UNAMITY. Use with live, attenuated vaccines during, or immediately prior to, UNAMITY therapy

is not recommended. Prior to initiating UNAMITY, 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 UNAMITY 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 UNAMITY 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 rheumatoid arthritis clinical trials. In treatment-naïve patients, combination with methotrexate resulted in increased frequency of hepatic transaminase elevations compared with UNAMITY monotherapy (see section 4.8).

If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, UNAMITY should be temporarily interrupted until this diagnosis is excluded.

Malignancy

The risk of malignancies including lymphoma is increased in patients with rheumatoid arthritis. Immunomodulatory medicines may increase the risk of malignancies including lymphoma.

The clinical data are insufficient to assess the potential incidence of malignancies following exposure to UNAMITY. Long-term safety evaluations are ongoing.

Venous Thromboembolism

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

UNAMITY 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, UNAMITY treatment should be temporarily interrupted and patients should be evaluated promptly, followed by appropriate treatment.

COVID-19

VTE prophylaxis is recommended unless contraindicated (see section 4.2).

There is limited information regarding use of baricitinib in patients with COVID-19 and any of the following clinical findings:

- concomitant active serious infections
- ANC < 1 x 10^9 cells/L
- ALC < 0.2 x 10^9 cells/L
- Haemoglobin < 8 g/dL

Patients with COVID-19 who require low-flow oxygen or non-invasive ventilation/high flow oxygen suffer from a serious, potentially life-threatening condition. Baricitinib should therefore only be used in patients with the above clinical findings if the potential benefits outweigh the potential risks.

Laboratory monitoring in patients with Rheumatoid Arthritis

Table 2: 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

Laboratory Measure	**Action**	**Monitoring Guidance**
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 medicines

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 UNAMITY with potent immunosuppressive medicines (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.

Diverticulitis

Events of diverticulitis and gastrointestinal perforation have been reported in clinical trials and from postmarketing sources. Baricitinib should be used with caution in patients with diverticular disease and especially in patients chronically treated with concomitant medications 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

UNAMITY contains less than 1 mmol sodium (23 mg) per tablet, i.e., essentially “sodium-free”.

4.5. Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

Immunosuppressive medicines

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

Potential for other medicines 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 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 UNAMITY exposure. Since dedicated interaction studies have not been conducted, caution should be used when leflunomide or teriflunomide are given concomitantly with UNAMITY.

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 UNAMITY 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 UNAMITY 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 UNAMITY with ketoconazole (strong CYP3A inhibitor) resulted in no clinically meaningful effect on the PK of baricitinib. Coadministration of UNAMITY with fluconazole (moderate CYP3A/CYP2C19/CYP2C9 inhibitor) or rifampicin (strong CYP3A inducer) resulted in no clinically meaningful changes to UNAMITY exposure.

Gastric pH modifying medicines

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

Potential for baricitinib to affect the pharmacokinetics of other medicines

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 UNAMITY was co-administered with digoxin (Pgp substrate) or methotrexate (substrate of several transporters).

Cytochrome P450 enzymes

In clinical pharmacology studies, coadministration of UNAMITY with the CYP3A substrates simvastatin, ethinyl estradiol, or levonorgestrel resulted in no clinically meaningful changes in the PK of these medicines.

4.6. Fertility, pregnancy and lactation

Pregnancy

Rheumatoid Arthritis: UNAMITY is contraindicated during pregnancy (see section 4.3). The JAK/STAT pathway has been shown to be involved in cell adhesion and cell polarity which can affect early embryonic development. 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.

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 UNAMITY the parents should be informed of the potential risk to the foetus.

COVID-19: The woman must be fully informed of the potential foeto-toxicity of UNAMITY and the potential efficacy benefits to herself. An appropriate treatment decision can then be made.

Breastfeeding

Women who are breastfeeding should not use UNAMITY (see section 4.3). 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.

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

UNAMITY 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 UNAMITY 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 UNAMITY treatment included herpes zoster.

In placebo controlled COVID-19 clinical trials, for up to 28 days, the most commonly reported ADRs occurring in ≥ 2 % of patients treated with UNAMITY were ALT ≥ 3 x ULN (18,0 %), AST ≥ 3 x ULN (11,5 %), thrombocytosis (8,2 %), CPK increase (3,7 %) and neutropenia (2,2 %).

Tabulated list of adverse reactions

Rheumatoid Arthritis: A total of 3,770 patients were treated with UNAMITY in clinical studies in rheumatoid arthritis representing 10,127 patient-years of exposure. Of these, 2,960 rheumatoid arthritis patients were exposed to UNAMITY for at least one year. Seven placebo-controlled studies were integrated 1,142 patients on 4 mg once daily and 1,215 patients on placebo) to evaluate the safety of UNAMITY in comparison to placebo for up to 16 weeks after treatment initiation.

COVID-19 *:* A total of 1,257 patients were treated with UNAMITY for up to 14 days in clinical studies in COVID-19.

Table 3: Represents integrated clinical trial data from rheumatoid arthritis through week 16

Body system/adverse drug reaction terms	**Very common ≥ 10 %**	**Common ≥ 1 % and < 10 %**	**Uncommon (Infrequent) ≥ 0,1 % and < 1 %**
Gastrointestinal disorders			
Nausea		X	
Abdominal pain[a]		X	
Infections and infestations			
Upper respiratory tract infections[b]	X		
Herpes simplex[c]		X	
Herpes zoster		X	

Body system/adverse drug reaction terms	**Very common ≥ 10 %**	**Common ≥ 1 % and < 10 %**	**Uncommon (Infrequent) ≥ 0,1 % and < 1 %**
Urinary tract infection		X	
Investigations			
Weight increased			X
Nervous system disorders			
Headache		X	
Vascular disorders			
Deep Vein Thrombosis			X
Respiratory, thoracic, mediastinal disorders			
Pulmonary embolism			X
Skin and subcutaneous tissue disorders			
Acne			X
Laboratory Parameters[d]			
Clinical Chemistry			
Creatine Phosphokinase > 5 x ULN			X
LDL cholesterol ≥ 130 g/dL (≥ 3,36 mmol/L)	X		
Triglycerides ≥ 500 mg/dL (≥ 5,65 mmol/L)			X
ALT ≥ 3 x ULN		X	
AST ≥ 3 x ULN			X
Haematology			
Neutropenia < 1000 cells/mm^3			X

Body system/adverse drug reaction terms	**Very common ≥ 10 %**	**Common ≥ 1 % and < 10 %**	**Uncommon (Infrequent) ≥ 0,1 % and < 1 %**
Thrombocytosis > 600,000 cells/mm^3		X	

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower.

[b] Includes acute sinusitis, chronic sinusitis, epiglottitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, tracheitis, upper respiratory tract infection.

[c] Includes eczema herpeticum, genital herpes, herpes simplex, Kaposi's varicelliform eruption, ophthalmic herpes simplex, oral herpes.

[d] As assessed by measured values within the clinical trial database. Frequencies are based on shifts from pre-treatment to post-treatment (with number at risk as the denominator), except for ALT and AST for which frequencies are based on observed elevation during treatment.

Lipids

Baricitinib treatment was associated with increase in lipid parameters including total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol. Elevations were observed at 12 weeks and remained stable thereafter in patients with RA.

COVID-19

In COVID-19 placebo-controlled studies, the proportion of infections in patients treated with baricitinib was 12,6 % compared to 14,5 % in the placebo group.

Treatment-emergent VTE was diagnosed in the baricitinib group in 3,3 % compared to 2,8 % in the placebo group. PE and DVT were reported in 1,4 % and 1,5 % of patients in the baricitinib group compared to 0,9 % and 1,3 % in the placebo group.

Low neutrophil and high platelet counts (thrombocytosis) were more frequent in the baricitinib treatment arm versus placebo (2,2 % versus 1,9 %, and 8,2 % versus 4,3 %, respectively).

ALT and AST ≥ 3 x ULN were reported in the baricitinib treated group for 18 % and 11,5 % of patients compared to 15,6 % and 9,1 % of patients in the placebo group, respectively.

POSTMARKETING DATA:

The following undesirable effects (adverse drug reactions) are based on post marketing spontaneous reports:

Skin and subcutaneous tissue disorders:

Rash: Common (≥ 1 % and < 10 %)

This includes rash, dermatitis, dermatitis contact, eczema, dermatitis allergic, rash maculo-papular, rash pruritic, rash pustular, drug eruption, rash erythematous, rash macular.

Swelling of the face: Uncommon (≥ 0,1 % and < 1 %)

Urticaria: Uncommon (≥ 0,1 % and < 1 %)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications – https://www.sahpra.org.za/Publications/Index/8.

Alternatively, suspected adverse reactions can be reported to the holder of the certificate of registration at ade_za@lilly.com.

4.9. Overdose

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. Adverse events were

comparable to those seen at lower doses and no specific toxicities were identified. 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 symptomatic and supportive treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological classification: A 3.1 Antirheumatics (anti-inflammatory agents)

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 IC50 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.

Baricitinib has been identified as a numb-associated kinase (NAK) inhibitor with high-affinity for AP2-associated protein kinase 1 (AAK1)-8.2 nM, BIKE-20 nM and GAK-120 nM. Specific NAK's AAK1 and GAK are linked to SARS-CoV-2 (COVID-19) entry in human cells.

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 baricitinib 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.

IgG antibodies against the S1/S2 antigens of COVID-19 were increased in a limited sample of moderate to severe hospitalised COVID-19 patients treated with baricitinib.

Lymphocytes

Mean absolute lymphocyte count increased by 1 week after starting treatment with baricitinib, 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 baricitinib and were maintained throughout dosing.

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.

COVID-19 biomarkers

Baricitinib reduces levels of cytokines and biomarkers implicated in COVID-19, including IL-6, IFN-γ, MCP-3, CXCL10, IL-10, MCP-2, CCL19, PTX3, and IL-27. In addition, markers that are decreased in moderate to severe COVID-19 patients were increased in response to baricitinib, and include CCL17, GDF2, and SCF.

Clinical efficacy

Rheumatoid Arthritis

The efficacy and safety of baricitinib 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 4). 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 4: Clinical Trial Summary

Study name (Duration)	**Population** (Number)	**Treatment arms**	**Summary of key outcome measures**
RA- BEGIN (52 weeks)	MTX-naïve[1] (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-IR[2] (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- IR[3] (684)	• Baricitinib 4 mg QD • Baricitinib 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)	• Baricitinib 4 mg QD • Baricitinib 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 methotrexate (+/- 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 include methotrexate, 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, methotrexate 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 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 or methotrexate monotherapy. In RA-BEAM, treatment with baricitinib 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 methotrexate was not required, 501 subjects randomized to baricitinib 2 mg or 4 mg received methotrexate as background therapy, and 303 received conventional DMARDs other than methotrexate (approximately half with methotrexate and half without). The most common concomitant DMARDs in these subjects were methotrexate (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 baricitinib 4 mg compared to placebo or methotrexate achieved remission, as defined by SDAI ≤ 3.3 and CDAI ≤ 2.8, at weeks 12 and 24 (Table 5).

In all 4 studies, a significantly higher proportion of patients treated with baricitinib 4 mg compared to placebo or methotrexate 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 5: Response, Remission and Physical Function

Study	**RA-BEGIN MTX-naïve**			**RA-BEAM MTX-IR patients**			**RA-BUILD cDMARD-IR**			**RA-BEACON TNF-IR patients**		
Treatment group	MTX	BARI 4 mg	BARI 4 mg + MTX	PBO	BARI 4 mg	ADA 40 mg Q2W	PBO	BARI 2 mg	BARI 4 mg	PBO	BARI 2 mg	BARI 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 %						

Study	**RA-BEGIN MTX-naïve**			**RA-BEAM MTX-IR patients**			**RA-BUILD cDMARD-IR**			**RA-BEACON TNF-IR patients**		
Treatment group	MTX	BARI 4 mg	BARI 4 mg + MTX	PBO	BARI 4 mg	ADA 40 mg Q2W	PBO	BARI 2 mg	BARI 4 mg	PBO	BARI 2 mg	BARI 4 mg
N	210	159	215	488	487	330	228	229	227	176	174	177
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):												

Study	**RA-BEGIN MTX-naïve**			**RA-BEAM MTX-IR patients**			**RA-BUILD cDMARD-IR**			**RA-BEACON TNF-IR patients**		
Treatment group	MTX	BARI 4 mg	BARI 4 mg + MTX	PBO	BARI 4 mg	ADA 40 mg Q2W	PBO	BARI 2 mg	BARI 4 mg	PBO	BARI 2 mg	BARI 4 mg
N	210	159	215	488	487	330	228	229	227	176	174	177
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; BARI = Baricitinib; 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

COVID-19

The efficacy and safety of baricitinib were assessed in 2 Phase III randomised, double-blind, placebo-controlled, clinical trials:

- ACTT-2, which evaluated the combination of baricitinib 4 mg + remdesivir compared to placebo + remdesivir,
- COV-BARRIER, which evaluated baricitinib 4 mg compared to placebo. Patients could remain on background therapy, as defined per local guidelines.

ACTT-2 study:

A randomised, double-blind, placebo-controlled clinical trial (ACTT2) evaluated baricitinib 4 mg once daily + remdesivir versus placebo + remdesivir in 1033 hospitalised adult patients with COVID-19. This included:

- 14 % of patients not requiring supplemental oxygen (OS 4),

- 55 % patients requiring low-flow supplemental oxygen (OS 5),
- 21 % patients requiring noninvasive ventilation or high-flow oxygen (OS 6),
- and 11 % patients requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) (OS 7).

Patients were randomised 1:1, stratified by disease severity at enrolment, to receive baricitinib + remdesivir (n=515) or placebo + remdesivir (n=518). Patients received the following regimen:

- Baricitinib 4 mg or placebo once daily (orally) for 14 days or until hospital discharge
- Remdesivir 200 mg on Day 1 followed by 100 mg once daily (via intravenous infusion) on subsequent days for a total treatment duration of 10 days or until hospital discharge.

The baseline mean age was 55 years with 30 % of patients aged 65 or older. 63 % of patients were male, 48 % were Caucasian, 15 % were Black, 10 % were Asian. The most common comorbidities were obesity (56 %), hypertension (52 %), and type 2 diabetes (37 %). Demographics and disease characteristics were balanced across the combination group and the placebo group.

The primary clinical endpoint was time to recovery within 29 days after randomisation, defined as either discharged from hospital (with or without limitations of activity and with or without home oxygen requirements) or hospitalised but not requiring supplemental oxygen and no longer requiring ongoing medical care. For the overall population, the median time to recovery was 7 days for baricitinib + remdesivir compared to 8 days for placebo + remdesivir [hazard ratio: 1.15 (95 % CI 1.00, 1.31); p=0.047]. The clinical benefit of baricitinib was most pronounced in patients requiring low-flow oxygen, noninvasive ventilation or high-flow oxygen (see Table 6). The median time to recovery for subjects requiring mechanical ventilation or ECMO was not estimable. There was no apparent benefit in median time to recovery for baricitinib + remdesivir (5 days) versus remdesivir (4 days) in patients not requiring supplemental oxygen (rate recovery ratio 0.88 [95 % CI 0.62–1.23].

Table 6: Recovery outcomes by Ordinal Score at Baseline for patients requiring supplemental oxygen-ACTT-2 trial[a]

	Ordinal Score at baseline					
	5		**6**		**7**	
	Low-flow oxygen		**Noninvasive ventilation or high-flow oxygen**		**Mechanical ventilation/ECMO**	
	BARI + RDV (n=288)	PBO + RDV (n=276)	BARI + RDV (n= 103)	PBO + RDV (n=113)	BARI + RDV (n=54)	PBO + RDV (n=57)
Number of recoveries	262	243	82	73	22	21
Median time to recovery (95 % CI) - days	5 (5, 6)	6 (5, 6)	10 (9, 13)	18 (13, 21)	NE (25, NE)	NE (26, NE)
Recovery Rate ratio (95 % CI) – days[a]	1.17 (0.98, 1.39)		1.51 (1.10, 2.08)		1.08 (0.59, 1.97)	

[a] Recovery rate ratio calculated from the stratified Cox model. Recovery rate ratios >1 indicate benefit for baricitinib + remdesivir. NE = not possible to estimate

Patients assigned to baricitinib + remdesivir were more likely to have a better clinical status (according to an 8-point ordinal scale) at Day 15 compared to patients assigned to placebo + remdesivir [odds ratio: 1.26 (95 % CI 1.01, 1.57); p=0.044].

The proportion of patients who died or progressed to noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation by Day 29 was lower in baricitinib + remdesivir (23 %) compared to placebo + remdesivir (28 %) [odds ratio: 0.74 (95 % CI 0.56, 0.99); p=0.040].

The Day 29 mortality in the overall population was 4,9 % for the baricitinib group vs. 7,8 % for the placebo group (hazard ratio, 0,63; [95 % CI 0,37 to 1,05]; p=0,075). The clinical benefit of baricitinib was most apparent in patients requiring low-flow oxygen, noninvasive ventilation or high-flow

oxygen (see Table below):

Table 7: 29 Day Mortality Outcomes by Ordinal Score at Baseline for patients requiring supplemental oxygen [a] -ACTT-2 Trial

	Ordinal Score at baseline					
	5		**6**		**7**	
	Low-flow oxygen		**Noninvasive ventilation or high-flow oxygen**		**Mechanical ventilation/ECMO**	
	BARI + RDV (n=288)	PBO + RDV (n=276)	BARI + RDV (n= 103)	PBO + RDV (n=111[~~3~~])	BARI + RDV (n=54)	PBO + RDV (n=57)
29-day mortality – N (%)	5 (1,9 %)	12 (4,7 %)	7 (7,5 %)	13 (13,0 %)	11 (21,6 %)	12 (22,6 %)
Hazard ratio (95 % CI)	0,4 (0,14; 1,14)		0,55 (0,22; 1,38)		1,00 (0,45; 2,22)	

[a] Hazard ratios for baseline ordinal scale subgroups are from unstratified Cox proportional hazards models. Percentages are from Kaplan-Meier methodology. The table includes patients who received at least one dose of study drug.

COV-BARRIER Study

COV-BARRIER evaluated baricitinib 4 mg once daily versus placebo in hospitalised adult patients with COVID-19. Patients could remain on background therapy, as defined per local guidelines, including corticosteroids, antimalarials, antivirals such as remdesivir, and/ or azithromycin. The most frequently used background therapies were :

- corticosteroids (79,3 % of patients; 91,3 % of those patients received dexamethasone)
- remdesivir (18,9 % of patients)

The NIAID 8-point Ordinal Scale (OS) was used to classify baseline disease severity. The trial enrolled 1525 hospitalised adult patients with COVID-19.

The baseline mean age was 58 years with 33 % of patients aged 65 or older. 63 % of patients were male, 62 % were Caucasian, 5 % were Black, 12 % were Asian. The most common comorbidities were hypertension (48,3 %), obesity (33,0 %), and type 2 diabetes mellitus (29,4 %). Demographics and disease characteristics were balanced across the baricitinib and placebo groups.

The primary clinical endpoint was the proportion of patients progressing to non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) or death by Day 28. There was no statistically significant difference between the baricitinib and placebo groups with respect to the primary endpoint (27,8 % vs 30,5 %, respectively (p = 0,180)).

The 28-day mortality in the overall population was 8,1 % for the baricitinib group vs. 13,1 % for the placebo group (38,2 % relative reduction; hazard ratio = 0,57; [95 % CI 0,41 to 0,78]; nominal p = 0,002). The clinical benefit of baricitinib was most apparent in patients requiring low-flow oxygen, noninvasive ventilation or high-flow oxygen (see Table 8 below).

Table 8 – Day 28 Mortality Outcomes by Ordinal Score at Baseline for patients requiring low-flow oxygen, non-invasive ventilation or high-flow oxygen [a] - COV-BARRIER Trial

	Ordinal Score at baseline			
	5		**6**	
	Low-flow oxygen		**Non-invasive ventilation or high-flow oxygen**	
	PBO (n=472)	BARI (n=490)	PBO (n=187)	BARI (n=183)
28-day mortality – N (%)	41 (8,7)	29 (5,9)	55 (29,4)	32 (17,5)
Hazard ratio (95 % CI), p-value	0,72 (0,45, 1,16) p = 0,112[b]		0,52 (0,33, 0,80) p = 0,007[b]	

[a] Hazard ratios for baseline ordinal scale subgroups are from unstratified Cox proportional hazards models. The table includes all randomised patients.

[b] Not adjusted for multiplicity.

Patients assigned to baricitinib were more likely to have a better clinical status (according to an 8-point ordinal scale) at Day 14 compared to patients assigned to placebo [odds ratio: 1,28 (95 % CI 1,05; 1,56); nominal p = 0,017].

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 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_{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 COVID-19 was 14,2 L/hr (CV = 37,3 %) and 10,8 hrs (CV = 28,0 %), respectively. C_{max} and AUC at steady state in patients with COVID-19 are 0,7-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_{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 and efficacy of baricitinib have not yet been established in a paediatric population (see section 4.2). Based on PK modeling, the pharmacokinetics of baricitinib is similar between paediatric patients 10 years of age and older and adult patients.

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 red blood cell parameters, lymphocytes, eosinophils and basophils as well as lymphoid depletion in organs/tissues of the immune system were observed in mice, rats and dogs.

Degeneration of the sternal growth plate was observed in some dogs 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).

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

- Microcrystalline cellulose
- Croscarmellose sodium
- Magnesium stearate
- Mannitol

Film coating

- Iron oxide red
- Lecithin
- Macrogol
- Polyvinyl alcohol
- Talc

- Titanium dioxide

6.2. Incompatibilities

Not applicable

6.3. Shelf-life

The shelf-life is 36 months.

6.4. Special precautions for storage

Store at or below 30 ºC.

Keep in the original packaging

KEEP OUT OF REACH OF CHILDREN

6.5. Nature and contents of container

Polyvinylchloride/polyethylene/polychlorotrifluoroethylene– aluminium blisters in cartons of 14, 18, 28, 56, 84 or 98 film-coated tablets. Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Eli Lilly (S.A.) (Pty) Ltd

First Floor, Golden Oak House, Ballyoaks Office Park,

35 Ballyclare Drive,

Bryanston,

Johannesburg,

South Africa

8. REGISTRATION NUMBER(S)

UNAMITY 2 mg film-coated tablets: 52/3.1/0231.229

UNAMITY 4 mg film-coated tablets: 52/3.1/0232.230

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 January 2021

10. DATE OF REVISION OF THE TEXT

04 February 2022