Baricitinix
Baricitinib

COMPOSITION
Baricitinix 2 mg Tablet : Each film-coated tablet contains Baricitinib INN 2 mg.

Baricitinix 4 mg Tablet : Each film-coated tablet contains Baricitinib INN 4 mg.

PHARMACOLOGICAL INFORMATION
Therapeutic class: Anti-Rheumatic

PHARMACOLOGICAL ACTION

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**

Pharmacodynamics

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.

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.

Pharmacokinatics

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.

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

SPECIFIC POPULATIONS

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 Cmax 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.

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)

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 Cmax) were generally within the inter-subject PK variability of baricitinib. Therefore, no dose adjustment is needed based on these patient factors.

THERAPEUTIC INDICATIONS

Baricitinib is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs. Baricitinib may be used as monotherapy or in combination with Methotrexate.

DOSAGE & ADMINISTRATION
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.

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.

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.

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.

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.

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.

ADVERSE REACTIONS

The most commonly reported adverse drug reactions (ADRs) occurring in ≥ 2 % of patients treated with Baricitinib 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 Baricitinib treatment included Herpes zoster.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients of Baricinix.

Pregnancy:
Baricitinib is contraindicated during pregnancy.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 **fetus.**

Breast-feeding:
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 Baricitinib therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility:
The effect of Bricitinib on human fertility has not been evaluated. 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.

DRUG INTERACTIONS:

Pharmacodynamics interaction

Immunosuppressive medicinal products:
Combination with biologic DMARDs or other JAK inhibitors has not been studied. Use of Baricitinib with potent immunosuppressive medicinal products such as Azathioprine, Tacrolimus, or Ciclosporin was limited in clinical studies of Baricitinib, and a risk of additive immunosuppression cannot be excluded.

Potential for other medicinal products to affect the pharmacokinetics of Baricitinib Transporters:

In vitro, Baricitinib is a substrate for organic anionic transporter (OAT)3, P-glycoprotein (Pgp), breast cancer resistance protein (BCRP) and multidrug and toxic extrusion protein (MATE)2-K. In a clinical pharmacology study, dosing of Probenecid (an OAT3 inhibitor with strong inhibition potential) resulted in approximately a 2-fold increase in $AUC_{(0-\infty)}$ with no change in t_{max} or C_{max} of Baricitinib. Consequently, the recommended dose in patients taking OAT3 inhibitors with a strong inhibition potential, such as probenecid, is 2 mg once daily. 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 did inhibit OAT1, OAT3, organic cationic transporter (OCT) 1, OCT2, OATP1B3, BCRP and MATE1 and MATE2-K. Clinically meaningful changes in the PK of medicinal products that are substrates for these transporters are unlikely, with the exception of OCT1 substrates. It cannot be ruled out that Baricitinib is a clinically relevant OCT1 inhibitor, 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.

WARNINGS AND PRECAUTIONS

Infections:
Baricitinib is associated with an increased rate of infections such as upper respiratory tract infections compared to placebo. In treatment naïve patients, combination with Methotrexate resulted in increased frequency of infections compared to Baricitinib monotherapy. The risks and benefts of treatment with Baricitinib should be carefully considered prior to initiating therapy in patients with active, chronic or recurrent infections. If an infection develops, the patient should be monitored carefully and Baricitinib therapy should be temporarily interrupted if the patient is not responding to standard therapy. Baricitinib treatment should not be resumed until the infection resolves.

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

Haematological abnormalities:
Absolute Neutrophil Count (ANC) < 1 x 109 cells/L, Absolute Lymphocyte Count (ALC) < 0.5 x 109 cells/L and haemoglobin < 8 g/dL were reported in less than 1% of patients in clinical trials. Treatment should not be initiated, or should be temporarily interrupted, in patients with an ANC < 1 x 109 cells/L, ALC < 0.5 x 109 cells/L or haemoglobin < 8 g/dL observed during routine patient management. 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. 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, Baricitinib treatment should be temporarily interrupted until the episode resolves.

Vaccination:
Use with live, attenuated vaccines during, or immediately prior to, Baricitinib therapy is not recommended.

Lipids:
Dose dependent increases in blood lipid parameters were reported in patients treated with Baricitinib compared to **placebo.** 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 Baricitinib therapy and thereafter patients should be managed according to international clinical guidelines for hyperlipidaemia. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined. Hepatic transaminase elevations: Increases in alanine transaminase(ALT) and aspartate transaminase (AST) to ≥ 5 and ≥ 10 x upper limit of normal (ULN) were reported in less than 1% of patients in clinical trials. In Treatmentnaïve patients, combination with **Methotrexate** resulted in increased frequency of hepatic transaminase elevations compared with Baricitinib monotherapy. If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, Baricitinib 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 insuffcient to assess the potential incidence of malignancies following exposure to Baricitinib.

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

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

OVERDOSAGE

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.

PHARAMCEUTICAL INFORMATION

Storage Condition:
Store in cool and dry place, away from light. Keep out of the reach of children.

Presentations & Packings:

Baricitinib 2 mg Tablet : Each commercial box contain 30 **tablets** in a Pot.

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Manufactured By

BEACON Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh