For the use of a registered medical practitioner or a Hospital or laboratory only.

COVINIB 2/4

1. Generic Name:

Baricitinib Tablets 2mg/ 4mg

2. Qualitative and quantitative composition:

Composition

Each film coated tablet contains:

Baricitinib…… 2 mg/ 4 mg

Excipients……..q.s.

Colours: Ferric Oxide Red U.S.P./NF and Titanium Dioxide I.P

3. Dosage form and strength:

Dosage form: Film coated tablet

Strength: 2 mg/ 4 mg

4. Clinical particulars:

4.1 Therapeutic indication:

Baricitinib in combination with Remdesivir, for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in hospitalized adults requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

4.2 Posology and method of administration:

Patient Selection

- Evaluate baseline eGFR, liver enzymes and complete blood count to determine treatment suitability and dose. Monitor closely patients with abnormal baseline and post-baseline, laboratory values. See Table 1 for dosage adjustments-for patients with laboratory abnormalities.
- Baricitinib is not recommended for:
  - Patients who are on dialysis, have end-stage renal disease (ESRD, eGFR <15 ml min/1.73 m^2) or have acute kidney injury.
  - Patients with known active tuberculosis.
- There is currently limited information on the use of Baricitinib in combination with systemic corticosteroids for treating patients with COVID-19. However, use of Baricitinib in patients receiving systemic corticosteroids is not precluded.

Adult Patients

- The recommended dosage in adults with eGFR ≥60 ml/min/1.73 m^2 is 4 mg once daily for 14 days of total treatment or until hospital discharge, whichever is first. See Table 1 for dosage adjustments-for patients with laboratory abnormalities.
- Dosage adjustments in patients with renal or hepatic impairment are recommended.
- Dosage adjustments due to drug interactions are recommended.

- In hospitalized patients with COVID-19, prophylaxis for venous thromboembolism (VTE) is recommended unless contraindicated.

Pediatric Patients

Limited data informing Baricitinib dosing in paediatric patients comes from ongoing clinical trials for other uses. Based on the available information, treatment for COVID-19 for paediatric patients under emergency use authorization from reported literature is as follows:

- The recommended dosage for patients 9 years of age and older is 4 mg once daily for 14 days total treatment or until hospital discharge, whichever is first.
- The recommended dosage for patients 2 years through less than 9 years of age is 2 mg once daily for 14 days of total treatment or until hospital discharge, whichever is first.
- Baricitinib is not authorized for patients younger than 2 years of age.
- Dosage adjustments in patients with renal or hepatic impairment are recommended (See Renal impairment, Hepatic impairment).

Table 1: Dosage adjustments for patients with Abnormal Laboratory Values

Laboratory Analyte	Laboratory Analyte Value	Recommendation
eGFR	60 mL/min/1.73 m^2	• Adults and paediatric patients: 9 years of age and older: No dosage adjustment • Paediatric patients 2 years to less than 9 years of age: 2 mg once daily
	30 to < 60 mL/min/l .73 m^2	• Adults and paediatric patients: 9 years of age and older: 2 mg once daily • Paediatric patients 2 years to less than 9 years of age: 1 mg once daily
	15 to < 30 mL/min1.73 m^2	• Adults and paediatric patients: 9 years of age and older: 1 mg once daily • Paediatric patients 2 years to less than 9 years of age: Not recommended
	< 15 mL/min/1.73 m^2	Not recommended
Absolute Lymphocyte Count CALC)	≥200 cells/µL	Maintain dose
	< 200 cells/µL	Consider interruption until ALC is ≥200 cells/µL
Absolute Neutrophil Count (ANC)	≥500 cells/µL	Maintain dose
	< 500 cells/µL	Consider interruption until ANC is ≥500 cells/µL

Aminotransferases	If increases in ALT or AST are observed and drug-induced liver injury (DILI) is suspected	Interrupt Baricitinib until .the diagnosis of DILI is excluded

Abbreviations: ALC = absolute lymphocyte count, ALT = alanine transaminase, ANC = absolute neutrophil count, AST = aspartate transaminase, DILI = drug induced liver injury, eGFR = estimated glomerular filtration rate, hrs = hours.

If a laboratory- abnormality is likely due to the underlying disease state, consider the risks and benefits of continuing Baricitinib at the same or a reduced dose.

Method of administration:

For oral use, Baricitinib tablets are given orally once daily either always with or without food.

Alternate Administration:

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

- Oral dispersion
- Gastrostomy tube (G tube)
- Nasogastric tube (NG tube)

Preparation for Alternate Administration:

*Oral administration of dispersed tablets in water***:**

For patients who are unable to swallow whole tablets, 1 mg and/or 2 mg Baricitinib tablet(s), or any combination of tablets necessary to achieve the desired dose up to 4 mg may be placed in a container with approximately 10 ml (5 ml minimum) of room temperature water, dispersed by gently swirling the tablet(s) and immediately taken orally. The container should be rinsed with an additional 10 ml (5 ml minimum) of room temperature water and the entire contents swallowed by the patient (see Table 2).

*Administration via gastrostomy feeding tube***:**

For patients with a gastrostomy feeding tube, 1 mg and/or 2 mg Baricitinib tablet(s), or any combination of tablets necessary to achieve the desired dose up to 4 mg may be placed in a container with approximately 15 ml (10 ml minimum) of room temperature water and dispersed with gentle swirling. Ensure the tablet(s) are sufficiently dispersed to allow free passage through the tip of the syringe. Withdraw entire contents from the container into an appropriate syringe and immediately administer through the gastric feeding tube. Rinse container with approximately 15 ml (10 ml minimum) of room temperature water, withdrawn the contents into the syringe and administer through the tube. (see Table 2).

*Administration via nasogastric feeding tube***:**

For patients with an enteral feeding tube, 1 mg and/or 2 mg Baricitinib tablet(s), or a combination of tablets necessary to achieve the desired dose may be placed into a container with approximately 30 ml of room temperature water and dispersed with gentle swirling. Ensure the tablet(s) are sufficiently dispersed to allow free passage through the tip of the syringe. Withdraw the entire contents from the container into an appropriate syringe and immediately administer through the enteral feeding tube. To avoid clogging of small diameter tubes (smaller than 12 Fr), the syringe can be held horizontally and shaken during administration. Rinse container with a sufficient amount (minimum of 15 ml) of room temperature water, withdraw the contents into the syringe and administer through the tube. (see Table 2).

Intact tablets are not hazardous. Tablets may be crushed to facilitate dispersion. It is unknown if powder from the crushed tablets may constitute a reproductive hazard to the preparer. Use proper control measures (e.g. ventilated enclosure) or personal protective equipment (i.e. N95 respirator).

Dispersed tablets are stable in water for up to 4 hours.

Table 2: Minimum Dispersion and Rinse Volume for Alternate Administration

Administration via	Dispersion Volume	Container Rinse Volume
Oral dispersion	10 mL	10 mL
Gastronomy tube (G tube)	15 mL	15 mL
Nasogastric tube (NG tube)	30 mL	15 mL

4.3 Contraindications:

Hypersensitivity to the active substance or to any of the excipients of Baricitinib Tablets.

There are no known contraindications for Baricitinib.

4.4 Special warnings and precautions for use:

There are limited clinical data available for Baricitinib used on COVID patients. Serious and unexpected adverse events may occur that have not been previously reported with Baricitinib use.

Serious Infections

Serious infections have occurred in patients receiving Baricitinib:

- Avoid the use of Baricitinib with known active tuberculosis.
- Consider if the potential benefits outweigh the potential risks of Baricitinib treatment in patients with active serious infections other than COVID-19 or chronic/recurrent infections.

Thrombosis

In hospitalized patients with COV1D-19, prophylaxis for VTE is recommended unless contraindicated. If clinical features of deep vein thrombosis/pulmonary embolism occur, patients should be evaluated promptly and treated appropriately.

Abnormal Laboratory Values

Evaluate at baseline and thereafter according to local patient management practice. Monitor closely when treating patients with abnormal baseline and post-baseline laboratory values.

See table 1 for dosage adjustment for patients with abnormal renal, haematological and hepatic laboratory values. Manage patients according to routine clinical guidelines.

Vaccinations

Avoid use of live vaccines with Baricitinib, until four weeks after stopping Baricitinib.

Hypersensitivity

If a serious hypersensitivity occurs, discontinue Baricitinib while evaluating the potential causes of the reaction.

4.5 Interaction with other medicinal products and other forms of interaction:

Strong OAT3 Inhibitors: Baricitinib exposure is increased when Baricitinib is co-administered with strong OAT3 inhibitors (such as probenecid). In patients taking strong OAT3 Inhibitors, such as probenecid, reduce the recommended dose as follows:

- If the recommended dose is 4 mg once daily, reduce dose to 2 mg once daily.
- If the recommended dose is 2 mg once daily, reduce dose to 1 mg once daily.
- If the recommended dose is 1 mg once daily, consider discontinuing probenecid.

Other JAK Inhibitors or biologic disease modifying anti-rheumatic drugs (DMARDs): Baricitinib has not been studied in combination with other JAK inhibitors or with biologic DMARDs (biologic treatments targeting cytokines, B-cells or T-cells).

4.6 Use in specific population

Pregnancy

Baricitinib should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. Consistent with the mechanism of action, embryo-fetal toxicities including skeletal anomalies and reduced fertility have been observed in animals dosed in excess of the maximum human exposure. The limited human data on use of Baricitinib in pregnant women are not sufficient to inform a drug-associated risk for major birth defects or miscarriage

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. Women of childbearing potential have to use effective contraception during and for atleast 1 week after treatment.

Nursing Mothers

It is unknown whether Baricitinib are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of Baricitinib in milk. A risk to newborns/infants cannot be excluded and 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

Renal Impairment

There are limited data for Baricitinib in patients with severe-renal impairment.

Baricitinib is not recommended for patients who are on dialysis, have severe ESRD, or have severe acute kidney injury.

- Baricitinib should only be used in adults and paediatric patients 9 years of age and older with eGFR 15 to <30 ml/min/1.73 m^2 if the potential benefit outweighs the potential risk.
- Baricitinib is not recommended for paediatric patients ages 2 years through less than 9 years of age with eGFR<30 ml/min/1.73 m^2

Hepatic Impairment

Baricitinib has not been studied in patients with severe hepatic impairment. Baricitinib should only be used in patients with severe hepatic impairment if the potential benefit outweighs the

potential risk. It is not known if dosage adjustment is needed in patients with severe hepatic impairment.

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:

Serious venous thrombosis, including pulmonary embolism, and serious infections have been observed in COVID-19 patients treated with Baricitinib and are known adverse event drug reactions of Baricitinib.

In placebo-controlled clinical trials, for up to 16 weeks, the most commonly reported 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 headache (3.8 %). Infections reported with Baricitinib treatment included herpes zoster (1.4 %). In placebo-controlled atopic dermatitis clinical trials, for up to 16 weeks, the most commonly reported ADRs occurring in ≥ 2 % of patients treated with monotherapy or in combination with topical corticosteroids were similar to those observed in rheumatoid arthritis, except for increased LDL cholesterol (13.2 %) and herpes simplex (6.1 %). In patients treated with baricitinib in the atopic dermatitis clinical trials, the frequency of herpes zoster was very rare.

Table 3: 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).

System Organ Class	**Very common**	**Common**	**Uncommon**
Infections and infestations	Upper respiratory tract infections	Herpes zoster[b] Herpes simplex Gastroenteritis Urinary tract infections Pneumonia[d]	
Blood and lymphatic system disorders		Thrombocytosis > 600 x 10^9 cells/L[a, d]	Neutropaenia < 1 x 10^9 cells/L[a]
Metabolism and nutrition disorders	Hypercholesterolaemia[a]		Hypertriglyceridaemia[a]
Nervous system disorders		Headache	

Gastrointestinal disorders		Nausea[d] Abdominal pain	Diverticulitis
Hepatobiliary disorders		ALT increased ≥ 3 x ULN[a, d]	AST increased ≥ 3 x ULN[a]
Skin and subcutaneous tissue disorders		Rash Acne[c]	
Immune disorders			Swelling of the face, Urticaria
Respiratory, thoracic, mediastinal disorders			Pulmonary embolism
Vascular disorders			Deep Vein Thrombosis
Investigations		Creatine phosphokinase increased > 5 x ULN[a, c]	Weight increased

[a] Includes changes detected during laboratory monitoring (see text below).

[b] Frequency for herpes zoster is based on rheumatoid arthritis clinical trials.

[c] Frequency for acne and creatine phosphokinase increased > 5 x ULN is based on the pooled rheumatoid arthritis and atopic dermatitis clinical trials. In patients treated with baricitinib in the rheumatoid arthritis clinical trials, the frequency of those events was uncommon.

[d] Frequency for pneumonia, thrombocytosis > 600 x 10^9 cells/L, nausea, and ALT ≥3 x ULN is based on the pooled rheumatoid arthritis and atopic dermatitis clinical trials. In patients treated with baricitinib in the atopic dermatitis clinical trials, the frequency of those events was uncommon.

4.9 Overdose:

In case of overdose patient should be monitored for signs and symptoms of adverse reaction.

Single doses up to 40 mg and multiple doses of up to 20 mg daily for 10 days have been administered in reported clinical trials without dose-limiting toxicity. Adverse events were comparable to those seen at lower doses and no specific toxicities were identified. Pharmacokinetic data of a single dose of 40 mg in healthy volunteers indicate that more than 90 % of the administered dose is expected to be eliminated within 24 hours. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

5. Pharmacological properties:

5.1 Pharmacodynamic properties

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 effect:

Baricitinib 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 1 hours after dosing which returned to near baseline by 24 hours. Similar levels of inhibition were observed using either IL-6 or TPO as the stimulus.

Immunoglobulins

Mean serum IgG, IgM, and IgA values decreased by 12 weeks after starting treatment with baricitinib, and remained stable at a lower value than baseline through at least 52 weeks. For most patients, changes in immunoglobulins 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.

Cardiac Electrophysiology

At a dose 10 times the maximum recommended dose, Baricitinib does not prolong the QT interval to any clinically relevant extent.

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 Cmax by up to 18 % and delayed tmax 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 reported 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. 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 principle 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.

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.

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

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.

ACTT-2 (Adaptive COVID-19 Treatment Trial 2) Study in Hospitalized Adults Diagnosed with COVID-19 Infection

A reported randomized, double-blind, placebo-controlled clinical trial (ACTT-2, NCT04401579) of hospitalized adults with confirmed SARS-CoV-2 Infection compared treatment with Baricitinlb, a JAK inhibitor, plus remdesivir, an anti-viral (combination group; n=515) with placebo plus remdesivir (placebo group; n=518). Patients had to have laboratory-confirmed SARS-CoV-2 Infection as well as at least one of the following to be enrolled in the trial: radiographic infiltrates by Imaging, $SpO_2 \leq 94\%$ on room air, a requirement for supplemental oxygen, or a requirement for mechanical ventilation. Patients treated with the combination received the following regimen:

Baricitinib 4 mg once daily (orally) for 14 days or until hospital discharge.

Remdesivir 200 mg on day 1 and 100 mg once daily (via Intravenous infusion) on subsequent days for a total treatment duration of 10 days or until hospital discharge.

Scientific Evidence supporting this Emergency Use Authorisation.

For the overall population (N=1033 patients) at randomization, mean age was 55 years (with 30% of patients aged 65 or older); 63% of patients were male, 51% were Hispanic or Latino, 48% were white, 15% were black or African American, and 10% were Asian; 14% did not require supplemental oxygen, 55% required supplemental oxygen, 21% required non-invasive ventilation or high-flow oxygen and 11% required invasive mechanical ventilation or ECMO. The most common comorbidities were obesity (56%), hypertension (52%), and type 2 diabetes (37%). Demographic and disease characteristic were balanced across the combination group and the placebo group.

The primary endpoint, for the intent to treat population, was time to recovery within 29 days after randomization. Recovery was defined as being discharged from the hospital with limitations on activities and/or requiring home oxygen or hospitalized but not requiring supplemental oxygen and no longer requiring medical care. The key secondary endpoint was clinical status on day 15 assessed on an 8 point ordinal scale (OS) consisting of the following categories:

1. Not hospitalized, no limitations on activities [OS-1];
2. Not hospitalized, limitations on activities and/or requiring home oxygen [OS-2];
3. Hospitalized, not requiring supplemental oxygen- no longer requires ongoing medical care [OS-3];
4. Hospitalized, not requiring supplemental oxygen- requiring ongoing medical care (COVID-19 related or otherwise) [OS-4];
5. Hospitalized, requiring supplemental oxygen [OS-5];
6. Hospitalized, on non-invasive ventilation or high- flow oxygen devices [OS-6];
7. Hospitalized, on invasive mechanical ventilation or ECMO [OS-7]; and
8. Death [OS-8]

For the overall population, the median time to recovery (defined as discharged from hospital of hospitalized but not requiring supplemental oxygen or ongoing medical care) was 7 days for Baricitinib + Remdesivir compared to 8 days for Placebo + Remdesivir [hazard ratio: 1.15 (95% CL 1.00, 1.31); p=0.047]

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% Cl 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% Cl 0.56, 0.99); p=0.039]. Patients who required non-invasive ventilation/high-flow oxygen or Invasive mechanical ventilation (including ECMO) at baseline needed to worsen by at least 1 point on an 8-point ordinal scale to progress.

Table 4: Comparisons and Confidence Intervals for Adverse Events in the As-treated Population[a,b]

Patients with at least 1:	**PBO + RDV (N = 509) n (%)**	**BARI + RDV (N = 507) n (%)**	**Risk Difference % (95% Cl)**
AE	242 (48)	210 (41)	-6 (-12, 0)
Grade 3-4 AE	238 (47)	207 (41)	-6 (-12, 0)
SAE	103 (20)	77 (15)	-5 (-10. 0)
SAE with fatal outcome	31 (6)	19 (4)	-2(-5.0)
AE leading to discontinuation of study drug	59 (12)	34 (7)	-5 (-8, -1)
Infections	50 (10)	32 (6)	-4 (-7, 0)
VTE	16 (3)	21 (4)	1 (-1, 3)
Pulmonary Embolism	2 (0.4)	5 (1)	0.6 (-0.4, 1.6)

[a]Abbreviations: AE = adverse event; BARI + RDV = Baricitinib plus remdesivir; NIAID = National Institute of Allergy and Infectious Disease**;** N = number of patients in the As Treated Population; n = number of patients reporting at least 1 event; PBO + RDV = placebo plus remdesivir; SAE = serious adverse event; VTE = venous thromboembolic events.

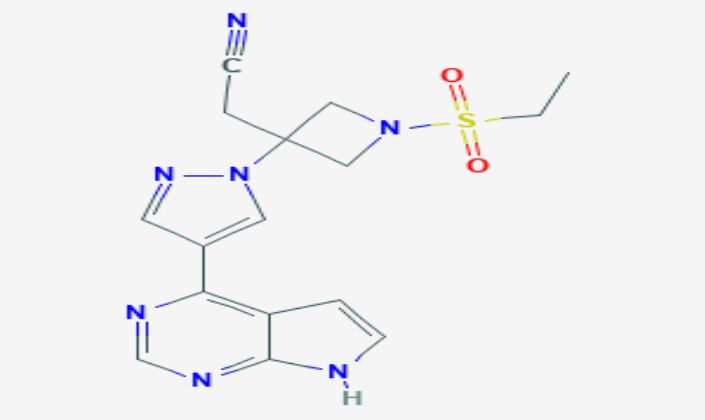
[b]Patients are counted once for each category regardless of the number of events.

6. Nonclinical properties:

Baricitinib, non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.
No evidence of tumorigenicity was observed in male or female rats that received Baricitinib for 91 to 94 weeks at oral doses up to 8 or 25 mg/kg/day respectively (approximately 12 and 55 times the MRHD on an AUC basis). Baricitinib tested negative in the in vitro bacterial mutagenicity assay (Ames essay), in vitro chromosome aberration assay, in human peripheral blood lymphocytes, and in vivo rat bone marrow micronucleus assay. Fertility (achievement of pregnancy) was reduced in male and female rats that-received Baricitinib at oral doses of 50 and 100 mg/kg/day respectively (approximately 113 and 169 times the MRHD in males and females, respectively, on an AUC basis).

7. Description:

Baricitinib is a Janus kinase (JAK) inhibitor with the chemical name {1-ethylsulfonyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl]acetonitrile. Baricitinib has an empirical formula of C_{16} $H_{17}N_7O_2S$ and a molecular weight is 371.42. Baricitinib, IUPAC name is ((2R, 3S, 4R, 5R)-3, 4-dihydroxy-5-(4-(hydroxyamino)-2-oxo-3, 4-dihydropyrimidin-1(2H)-yl) tetrahydrofuran-2-yl) methylisobutyrate. Baricitinib has the following structural formula:



8. Pharmaceutical particulars:

8.1 List of excipients

Microcrystalline Cellulose, mannitol, croscarmellose sodium and magnesium stearate, Opadry Brown (03F565212)

8.2 Incompatibilities:

Not applicable.

8.3 Shelf-life:

Please see manufacturing date and expiry date printed on pack.

Do not use later than the date of expiry date which is stated on the packaging.

The expiry date refers to the last day of that month.

8.4 Packaging information:

2mg : HDPE bottle, containing 14 tablets. Each carton contains one bottle with pack insert.

4mg : HDPE bottle, containing 14 tablets. Each carton contains one bottle with pack insert.

8.5 Storage and handing instructions:

Do not store above 30°C. Protect from moisture and direct light.

Keep all medicines out of reach and sight of children.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

BDR Pharmaceuticals International Pvt. Ltd.

At : Plot No. 65, 66, 67, Phase II, Atgaon Industrial Complex,

Atgaon, Shahapur (Thane) - 421601

11. Details of permission or licence number with date

MH/103403A

12. Date of first revision/ last version

June 2021

MARKETED BY

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