Baricitinib in the treatment of adult patients with COVID-19

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Useful elements are provided below to guide the prescription and to define a relationship between the benefits and risks of the medicine for the individual patient.	
For which patients is it recommended?	In light of current knowledge, as well as the potential lack of alternatives already available in Law 648/96 for the same indication, baricitinib can be used for the treatment of adults hospitalized with severe COVID-19, in high-flow oxygen therapy or in non-invasive mechanical ventilation, and/or with high levels of systemic inflammation indices. In particular, hospitalised patients with rapidly deteriorating clinical conditions are considered candidates for treatment with baricitinib: • Recently hospitalised patients with rapidly increasing oxygen requirements who need non-invasive mechanical ventilation or high flow oxygen in the presence of high levels of inflammation indices (CRP ≥75 mg/L). Co-administration with interleukin inhibitors or other JAK inhibitors is not allowed.
At what dosages is it preferably prescribed and in what forms?	***Recommended dosage*** The recommended dosage of baricinib in adult patients is 4 mg administered orally once a day for a maximum duration of 14 days (or until hospital discharge for clinical resolution, if earlier). For particular situations, please refer to the technical data sheet of the drug Olumiant®; in particular the dosage of Olumiant® depends on the eGFR values: • if eGFR 30- <60 mL / min / 1.73m^2: 2 mg PO QD • if eGFR <30 mL / min / 1.73m^2: do not administer
Who can prescribe the medicine in this emergency phase?	Baricitinib (Olumiant®) is a prescription-only hospital drug. For the indication admitted for reimbursement in Law 648/96, the prescription is limited to clinicians operating in the centres indicated by the Region for the management of COVID-19.
What are the greatest risks in terms of adverse reactions?	**Warnings** (from data sheet)**:** • Neutropenia and severe infections • Hepatic events • Diverticulitis and gastrointestinal perforation • Venous thromboembolism For further safety information please refer to the drug technical data sheet

	https://www.ema.europa.eu/en/documents/product-information/olumiant-epar-product-information_en.pdf
Can it be prescribed together with other medicines?	**Main interactions** (from data sheet)**:** Concomitant treatment of baricitinib with biologic DMARDs, biologic immunomodulators or other Janus kinase (JAK) inhibitors and TNF-alpha antagonists is not recommended. For more information on drug interactions, please refer to the technical data sheet and check the website: https://www.covid19-druginteractions.org/

Background

Baricitinib (Olumiant®) is a selective and reversible inhibitor of Janus kinase (JAK)1 and JAK2, intracellular enzymes involved in the signal transmission of cytokines and growth factors, involved in hematopoiesis and in the immune response.

Baricitinib is authorised by the EMA for the following clinical conditions:

- Treatment of moderate to severe active rheumatoid arthritis in adult patients with an inadequate response, or intolerant to one or more disease-modifying anti-rheumatic drugs. Olumiant® can be administered plain or in combination with methotrexate;
- Treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy (this indication is currently not reimbursed in Italy).

Rationale

The rationale for using baricitinib in patients with SARS-CoV-2 infection is based on a dual activity of reducing the inflammatory response and reducing viral endocytosis.

Baricitinib was the first drug identified, with artificial intelligence, as a potentially useful molecule in patients with COVID-19, for a dual action of mitigation of the inflammatory cascade and reduction of virus entry into lung cells (*Richardson P et al. Lancet 2020*).

The receptor used by the SARS-CoV2 virus to infect lung cells is the ACE2 receptor, a surface protein exposed on kidney, blood, heart, and alveolar epithelial cells. One of the known regulators of endocytosis is the protein kinase 1 associated with AP2 (AAK1), towards which baricitinb has a high affinity.

Main evidence available

Randomised clinical trials

- 01/09/2021 – Marconi VC et al. for the COV-BARRIER Trial. Lancet Respir Med 2021. This is a randomised, double-blind, placebo-controlled clinical trial (NCT04421027). Subjects eligible for enrolment in the clinical study were hospitalised adults with a laboratory confirmed SARS-CoV-2 infection, pneumonia or symptomatic active COVID-19 disease (with clinical symptoms including one of the following: fever, vomiting, diarrhoea, dry cough, tachypnea) and at least one elevated inflammatory marker (CRP, D-dimer, LDH, ferritin). On the other hand, subjects requiring invasive mechanical ventilation were excluded (NIAID-OS score 7). Following the publication of the results of the ACTT-2 study, the COV-BARRIER study was amended (as of October 2020) to limit enrolment only to those who required oxygen

support at the baseline (NIAID-OS score 5-6). Enrolled subjects were randomized 1: 1 to receive 4 mg baricitinib once daily (n = 764) or placebo (n = 761), both in addition to basic standard of care treatment, as defined by local guidelines, which included predominantly corticosteroids (79% of patients, mainly dexamethasone) and remdesivir (19% of patients).

In the period 11/06/2020-15/01/2021, 1525 patients were enrolled, with an average age of 58 years (33% of patients aged 65 or over): 12% did not require supplementation oxygen (OS 4), 63% required supplemental oxygen (OS 5), 24% required high flow oxygen or non-invasive ventilation (OS 6). The most common comorbidities were hypertension (48%), obesity (33%) and type 2 diabetes (29%). Demographic and clinical characteristics were balanced between the study groups.

The primary composite endpoint was the percentage of patients who progressed to high-flow oxygen/non-invasive ventilation (OS6) or invasive mechanical ventilation/ECMO (OS 7) or to death (OS 9) within the first 28 study days. The main secondary endpoint was all cause mortality by day 28. The estimated percentage of patients who died or switched to high flow oxygen/non-invasive ventilation or invasive mechanical ventilation was lower in patients treated with baricitinib (27.8%) compared to placebo (30.5%), but this effect was not statistically significant [OR 0.85 (95% CI 0.67, 1.08); p = 0.180]. The percentage of patients who died by day 28 was 8.1% (62/764) for baricitinib vs. 13.3% (101/761) for placebo [HR 0.57 (95% CI: 0.41, 0.78)], with a relative reduction in mortality of 32%. The advantage in terms of mortality reduction was also confirmed at 60 days (10% vs 15%; HR 0.62; 95% CI 0.47-0.83). In all specified severity subgroups, mortality estimates were numerically lower among subjects receiving baricitinb compared to placebo. The difference in mortality was more pronounced in the subgroup of 370 subjects receiving high-flow oxygen or non-invasive ventilation at baseline (17% vs 29.4%; HR 0.25; 95% CI 0.33-0.80).

- 11/12/2020 – Kalil AC et al. for the ACTT-2 Study. NEJM 2020. This is a randomised, double-blind, placebo-controlled clinical trial (ACTT-2, NCT04401579). Adult subjects with laboratory confirmed SARS-CoV-2 infection and at least one of the following parameters were eligible for study: radiographic infiltrates, SpO2 ≤94% in ambient air, need for supplemental oxygen, or mechanical ventilation or ECMO. Enrolled subjects were randomized (1: 1) to receive remdesivir (200 mg on Day 1 and 100 mg once daily for up to 10 days) + placebo or remdesivir (at the same dose) + baricitinib (4 mg once per day, orally, for 14 days or until hospital discharge). In the period May-July 2020, 1033 subjects were randomised: 515 in the remdesivir+baricitinb combination group and 518 in the remdesivir + placebo group. The average age of the study population was 55 years (with 30% of patients aged 65 or over); 14% did not require supplemental oxygen, 55% required supplemental oxygen, 21% were on non-invasive ventilation or high-flow oxygen and 11% were on invasive mechanical ventilation or ECMO. The most common comorbidities were obesity (56%), hypertension (52%) and type 2 diabetes (37%). The main demographic and clinical characteristics were balanced between the two study groups.

  The primary endpoint, for the intention-to-treat population, was recovery time within 29 days after randomization defined as the first day category 1 (discharge from hospital with no activity limitations), 2 (discharge from hospital with activity limitations and/or with home oxygen) or 3 (hospitalisation but without the need for supplemental oxygen or medical treatment) on the ordinary 8-category scale. The mean recovery time (primary endpoint) was 7 days for baricitinib + remdesivir versus 8 days for placebo + remdesivir (RR 1.15; 95% CI 1.00, 1.31; p = 0.047). Patients assigned to baricitinib + remdesivir were also more likely to have better clinical status (according to the 8-point ordinal scale) on Day 15 than patients assigned to placebo + remdesivir (OR 1.26; 95% CI 1.01, 1.57; p = 0.044). The percentage of patients who died or switched to non-invasive/high flow oxygen or invasive mechanical ventilation on Day 29 was lower in the baricitinib + remdesivir group (23%) compared to placebo + remdesivir (28%)

(OR 0.74; 95% CI 0.56, 0.99; p = 0.039). The percentage of patients who died by day 29 was 4.7% (24/515) for baricitinib + remdesivir vs 7.1% (37/518) for placebo + remdesivir.

Scientific reviews and meta-analyses

Scientific reviews and meta-analyses updated in real time have been made available ("*living systematic review and network meta-analysis*") which have been conducted by important research groups in which the results of the clinical studies were summarised as available at any given time.

- In one of the main available living systematic reviews, edited by the Cochrane in collaboration with several universities and research bodies (https://covid-nma.com/living_data/index.php), the analysis of the available data deriving from RCT, updated on 22/09/2021, confirms a protective effect of baricitinib on mortality outcomes both in monotherapy (RR 0.62; 95%CI 0.46-0.83 vs placebo) and in combination with remdesvir (RR 0,65; 95%CI 0,40-1,07 vs remdesivir).
- In a recent meta-analysis that included 4,363 COVID-19 patients treated with JAK inhibitors, their use was associated with an increased recovery rate (RR 1.17; 95% CI: 1.01-1, 36), at a shorter recovery time (mean difference -0.96; 95% CI: -1.15-0.77), at a reduced risk of clinical deterioration (RR 0.66; 95% CI: 0, 48-0.89); and a reduced mortality rate (RR 0.52; 95% CI: 0.36–0.76) (*Limen RY et al. 2021*).

Recommendations by international organisations

- **National Institutes of Health (NIH)**: *[section last reviewed and updated 8/25/2021]*:

  In newly hospitalised subjects with rapidly increasing oxygen requirements who need non-invasive mechanical ventilation or high-flow oxygen in the presence of high levels of inflammation indices, the expert panel recommends the use of baricitinib in addition to dexamethasone or dexamethasone + remdesivir (Recommendation BIIa).

- **Infectious Diseases Society of America (IDSA)** *[section last reviewed and updated 8/21/2021]*:

  Recommendation #17: In hospitalised adults with severe COVID-19 and with high inflammatory markers but not undergoing invasive mechanical ventilation, the IDSA panel of experts recommends the use of baricitinib (Conditional recommendation, moderate certainty of evidence).*

  Remarks:

  • Baricitinib 4 mg daily for up to 14 days or until hospital discharge.

  • Baricitinib appears to show the greatest benefit in patients with severe COVID-19 on high-flow oxygen/non-invasive ventilation at baseline.

  • Patients receiving baricitinib for COVID-19 treatment should not receive tocilizumab or other IL-6 inhibitors.

  Recommendation #18: In hospitalised patients with severe COVID-19 who cannot receive corticosteroid therapy (which is the standard of care) due to a contraindication, the IDSA panel suggests using baricitinib with remdesivir rather than remdesivir alone (Conditional recommendation, low certainty of evidence).*

  Remark:

  - *The benefits of baricitinib + remdesivir for people on mechanical ventilation are uncertain.*

** Severe disease refers to patients with SpO2 ≤94% in ambient air, including patients receiving supplemental oxygen, oxygen through a high-flow device or non-invasive ventilation*

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