Sarilumab 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, it is believed that sarilumab can be used as an alternative to tocilizumab when the latter is not available, for the treatment of hospitalised adults with severe COVID-19 and/or with high levels of systemic inflammation indices. In particular, hospitalised patients with rapidly deteriorating clinical conditions are considered eligible for treatment with sarilumab: • Recently hospitalised patients admitted to intensive care for less than 24/48 hours who receive mechanical ventilation or high-flow oxygen; or recently hospitalized patients with rapidly increasing oxygen requirements who require non-invasive mechanical ventilation or high-flow oxygen with high levels of inflammation indices (CRP ≥75 mg/L). • Hospitalised patients in rapid clinical progression after 24/48 hours of use of dexamethasone, or other cortisone. Rapid clinical progression means rapidly increasing oxygen requirements, even without the need for non-invasive ventilation or high flow oxygen, and with 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 sarilumab for the treatment of COVID-19 in adult patients is **400 mg** administered by **intravenous infusion** lasting at least 60 minutes. *Sarilumab is available as a pre-filled syringe. For a 400 mg dose, two 200 mg pre-filled syringes should be injected into a 100 ml infusion bag of 0.9% sodium chloride (turn the bag upside down at least 10 times to ensure thorough mixing).*
Who can prescribe the medicine in this emergency phase?	Sarilumab (Kevzara®) 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)**:** • Active infections in place (other than COVID-19) that could worsen with the use of sarilumab • Latent or active tuberculosis

	• Neutropenia (neutrophils <2 x 10^9/L) and thrombocytopenia (platelets <150 x 10^3/μL) • History of intestinal ulceration or diverticulitis • Active liver disease and hepatic impairment For further safety information please refer to the drug technical data sheet https://www.ema.europa.eu/en/documents/product-information/kevzara-epar-product-information_en.pdf
Can it be prescribed together with other medicines?	**Main interactions** (from data sheet)**:** Blocking IL-6 signalling by interleukin 6 (IL6Rα) receptor antagonists such as sarilumab may reverse the inhibitory effect of IL-6 and restore CYP activity, leading to altered drug concentrations. Modulation of IL-6 effect on CYP enzymes by sarilumab may be clinically relevant for CYP substrates with a narrow therapeutic index, in which the dose is individually adjusted. Upon initiation or discontinuation of Kevzara therapy in patients treated with medicinal products that are CYP substrates, therapeutic monitoring should be performed of effect (e.g. warfarin) or of drug concentration (e.g. theophylline) and the individual dose of the medicinal product should be adjusted as needed. Care must be taken with patients initiating treatment with Kevzara while on CYP3A4 substrate therapy (e.g. oral contraceptives or statins), as Kevzara may reverse the inhibitory effect of IL-6 and restore activity of CYP3A4, leading to a reduction in drug exposure and activity of the CYP3A4 substrate drug. For more information on drug interactions, please refer to the technical data sheet and check the website: https://www.covid19-druginteractions.org/

Background

Sarilumab (Kevzara®) is a human monoclonal antibody (IgG1 subtype) that binds specifically to both soluble and membrane-bound IL-6 (IL-6Rα) receptors and inhibits the signals they mediate.

Sarilumab is authorised by the EMA for the following indication: "*Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate*".

Rationale

The rationale for using sarilumab in complex patients with SARS-CoV-2 infection is based on the ability to block the IL-6 receptor (IL-6R), thus preventing the effects of activating the pro-inflammatory cascade. IL-6 represents the target of a potential therapeutic strategy in the treatment of severe and critical cases of patients affected by COVID-19. Infection with SARS-CoV-2 induces, in fact, an excessive and aberrant immune response of the host, associated with an acute respiratory distress syndrome and, in most critically ill patients, a "cytokine storm" (increased plasma and tissue levels of various cytokines that produce long-term damage and fibrosis of lung tissue). Numerous studies have shown a correlation between IL-6 levels and faster progression of SARS-CoV-2 disease *(Mojtabavi H et al. 2020).* It has been hypothesized that therapies targeting the cytokines involved in this aberrant inflammatory response (including IL-6) may have an

important therapeutic role in delaying lung damage in patients with SARS-CoV2 infection (*Angriman F et al. 2021; Potere N et al. 2021*).

Main evidence available

Randomised clinical trials

25/06/2021: (*Derde LPG et al. for the REMAP-CAP medRxiv 2021 preprint*): On June 25, the final results were made available in pre-print form relating to the domain of immunomodulatory therapies (anti-IL-6, and anti-IL-1) of the REMAP-CAP study (Randomised, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia), a large open-label, multi-domain, adaptive trial platform aimed at evaluating the efficacy of different therapeutic options for hospitalised COVID-19 patients. The domain related to immunomodulatory therapy involved the enrolment of adult subjects admitted to intensive care, who, within 24 hours of starting organ support therapy, were randomized to tocilizumab (8mg / kg; n = 952), sarilumab (400 mg; n = 485), anakinra (300 mg loading-dose followed by 100 mg every 6 hours for 14 days; n = 373), interferon beta (n = 21) or standard non-immunomodulatory therapy (n = 418) . All subjects, except 4, received respiratory support upon enrollment, mainly non-invasive or invasive mechanical ventilation in 42.9% and 32.9% of subjects, respectively. Concomitant steroid therapy was taken in 81.3% of the participants and remdesivir in 28.6% of cases.

The median number of days without organ support was 7 (IQR -1, 16), 9 (IQR -1, 17), 0 (IQR -1, 15), and 0 (IQR -1, 15, respectively) days for tocilizumab, sarilumab, anakinra and control arm. Corresponding adjusted ORs were 1.46 (95% CrI 1.13, 1.87), 1.50 (95% CrI 1.13, 2.00) and 0.99 (95% CrI 0.74, 1.35) for tocilizumab, sarilumab and anakinra, with probability of posterior superiority of 99.8%, 99.8% and 46.6%, compared to the control. Considering survival, the adjusted ORs were 1.42 (95% CrI 1.05.1.93), 1.51 (95% CrI 1.06, 2.20) and 0.97 (95% CrI 0.66 , 1.40) for tocilizumab, sarilumab, and anakinra, respectively, compared to control, resulting in 98.8%, 98.8%, and 43.6% posterior probability of superiority over control.

The REMAP-CAP immunomodulatory domain results suggest that, in patients with severe COVID-19 receiving organ support, tocilizumab and sarilumab are equally effective in improving survival and reducing the duration of organ support.

- 25/02/2021: *Gordon AC et al for the REMAP-CAP Investigators; NEJM 2021*: the first results are published which refer to the domain of immunomodulatory therapies (anti-IL-6) of the REMAP-CAP study (Randomised, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia), relating to the enrolment of adult subjects admitted to intensive care, who, within 24 hours from initiation of organ support therapy, were randomised to tocilizumab (8mg/kg iv; n = 353), sarilumab (400 mg iv; n = 48), or standard non-immunomodulatory therapy (n = 402). All subjects, except 3, received respiratory support upon enrolment: high flows with nasal cannula in 29% of cases, non-invasive or invasive mechanical ventilation in 42% and 29% of subjects, respectively. Compared to the primary endpoint (represented by an ordinal scale combining hospital mortality and organ-free days up to observation day 21), the study data yielded an estimated odds ratio of 1.46 (95% CI 1.25- 2.24) and 1.76 (95% CI 1.17-2.91) for greater efficacy associated with tocilizumab and sarilumab respectively compared with no immune modulation, with a high degree of statistical certainty (with a probability of being greater than no immune modulation by 99.9% for tocilizumab and 99.5% for sarilumab). In particular, the number of days without organ support was 10 (IQR, -1 to 16) in the tocilizumab-treated group, 11 (IQR, 0-16) in the sarilumab-treated group and 0 (IQT, -1 to 15) in the placebo group. Hospital mortality was 28% (98/350) for TCZ, 22.2% (10/45) for sarilumab and 35.8% (142/397) for the control group (with a statistically significant difference).
- 04/03/2021: *Lescure FX et al. Lancet Respir Med 2021*: a phase III, randomized, double-blind study conducted in 45 clinical centres in Argentina, Brazil, Canada, Chile, France, Germany, Japan, Israel, Italy,

Russia and Spain. The study included adults with a confirmed diagnosis of SARS-CoV-2 infection and a diagnosis of pneumonia, with severe COVID-19 disease (in non-high-flow oxygen therapy) or critical (in high-flow oxygen therapy, mechanical ventilation or those admitted to intensive care). In the period March-July 2020, 416 subjects were enrolled, randomised in a 2: 2: 1 ratio to sarilumab 400 mg iv (n = 173), sarilumab 200 mg iv (n = 159) or placebo (n = 84). At baseline, the majority (61%) of participants had severe, non-critical illness, with an SpO2/FiO2 ratio of 237.5. The distribution of concomitant therapies was homogeneous across the study arms, with a prevalence of use of corticosteroid therapy throughout the study (over 60% of participants had taken at least one dose of corticosteroids before, during, or after drug infusion in the studio). In the assessment of the study primary endpoint, which is time to improvement of at least two points on a 7-point ordinal scale, there were no significant differences (sarilumab 200 mg vs placebo: 10 days vs 12 days with a HR 1.03; 95 % CI 0.75-1.40; sarilumab 400 mg vs placebo: 10 days vs 12 with HR 1.1; 95% CI 0.84-1.54). The proportion of subjects alive at day 29 was also similar in the three groups (92% [77/84] in the placebo group; 90% [143/159] in the sarilumab 200 mg group; and 92% [159/173] in the sarilumab 400 mg group). On the other hand, on day 29 patients with critical illness showed a numerical difference, albeit not statistically significant, in terms of survival between sarilumab 400 mg (88%) and placebo (79%; difference + 8.9% [95% CI -7.7 to 25.5]; p = 0.25). Treatment-related adverse events were reported by 55/84 (65%) subjects in the placebo group, 103/159 (65%) in the sarilumab 200 mg group, and 121/173 (70%) in the sarilumab 400 mg group.

- 19/06/2021: *Sivapalasingam S et al. medRxiv 2021*: this is an adaptive, phase 2/3, randomised, double-blind study, currently only available in pre-print form. The phase 3 study involved a first cohort in which subjects receiving mechanical ventilation were randomised to sarilumab 200 mg (arm subsequently deleted after an interim analysis of the phase 2 study), to sarilumab 400 mg or to placebo. The primary analysis of phase 3 of the study was conducted in the subset of subjects under mechanical ventilation (n = 298). The primary endpoint was the proportion of subjects with ≥1 point of improvement in clinical status (equivalent, for the selected population, to being alive without receiving MV) at day 22, and was 43.2% in the sarilumab 400 mg arm and 35.5% in the placebo arm (difference in risk [RD] + 7.5%; 95% CI -7.4 to 21.3; P = 0.3261), equivalent to improvement in relative risk of 21.7%. All cause mortality at day 29 was 36.4% in the sarilumab 400 mg group compared to 41.9% in the placebo group (RD –5.5%; 95% CI, –20.2 to 8, 7; with a relative risk reduction of 13.3%). In the phase 2 and 3 post hoc pooling analyses of critically ill patients treated with MV, treatment with sarilumab 400 mg was associated with a lower risk of death than placebo (HR 0.76; 95% CI, 0.51- 1.13); this effect was also more evident in patients receiving corticosteroids at baseline (HR 0.49; 95% CI, 0.25 to 0.94). Upon interpreting the results of this study, which is only available in pre-print with incomplete access to all the results quoted, some important limitations must be considered, such as the fact that the primary analysis concerns only a subgroup of the enrolled population and that the prevalence of corticosteroid use was globally low and was not homogeneous between the study groups -in the subgroup of subjects on whom the primary analysis was performed (33.9% in the placebo group; 24.0% in the sarilumab 200 mg group and 28.8% in the sarilumab group 400 mg).

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 17/09/2021, the use of sarilumab is associated with a protective effect considering as outcome the time to clinical improvement (RR 1.27; 95% CI 1.05-1.53)

and time to death (RR 0.66; 95% CI 0.52-0.83), while for mortality outcome (RR 0.94; 95% CI 0.63-1.41) and improvement at 28 days (RR 0.98; 95% CI 0.87-1.10) the effect did not reach statistical significance.

- 06/07/2021 – WHO REACT Working Group: this is a large meta-analysis aimed at evaluating the efficacy of IL-6 antagonists in patients hospitalised for COVID-19, considering mortality at 28 days as the primary outcome. The meta-analysis was conducted on 27 studies (9 of which published), for a total of 10,930 patients (mean age, 61 years; 33% women). At 28-day follow-up, 1,407 deaths were recorded among 6,449 patients treated with IL-6 antagonists and 1,158 deaths among 4,481 patients treated with SoC or placebo therapy (OR 0.86 [95% CI, 0.79 -0.95]; P = .003). Considering the mortality impact of the two main IL-6 antagonists under study, the effect was more pronounced for tocilizumab (OR 0.83; 95% CI, 0.74-0.92; P <0.001) than for sarilumab (OR 1.08; 95% CI, 0.86-1.36; P = 0.52). Similarly, IL-6 therapy was associated with a reduced risk of progression to invasive mechanical ventilation or death, compared with routine care or placebo (OR 0.77; 95% CI, 0.70-0.85 for the cumulative class; OR 0.74, 95% CI, 0.66-0.82 for tocilizumab and OR 1.00; 95% CI, 0.74-1.34 for sarilumab). Statistically, the risk of secondary infections within 28 days was not significantly different between the placebo group (17.6%) and the IL-6 antagonist group (21.9%) (OR 0.99; 95% CI, 0.85-1.16). When interpreting meta-analysis data in the indirect comparison between tocilizumab and sarilumab, one should consider that the studies with sarilumab, overall less numerous, were conducted earlier in the outbreak, in a period prior to the recommendation on use of corticosteroids, whose prevalence of use was in fact lower in subjects treated with sarilumab than in those treated with tocilizumab.

Recommendations by international organisations

- **WHO** (*last update: July 6, 2021; last accessed: 18/09/2021*): The WHO panel of experts has given a strong recommendation for the use of IL-6 inhibitors (without distinction between tocilizumab and sarilumab) for the treatment of people with severe or critical COVID-19. The panel specifies that there are no reasons to differentiate the two drugs in practice with the exception of the pediatric population, for whom tocilizumab is used in the licensed indications and should therefore be preferred over sarilumab.
- **US National Institutes of Health (NIH)** (*last update: August 25, 2021; last accessed: 18/09/2021*): the use of sarilumab IV is considered as an alternative to tocilizumab, when the latter is not available, to the treatment of hospitalised patients who require high-flow oxygen therapy or mechanical ventilation/ECMO, in addition to dexamethasone.
- **Infectious Diseases Society of America (IDSA)** *(last accessed: 18/09/2021)*: The expert panel considers the data available insufficient to make recommendations regarding the use of sarilumab.
- **UK NHS Interim Position Statement**: *Interleukin-6 inhibitors (tocilizumab or sarilumab) for patients admitted to ICU with COVID-19 pneumonia (adults) – September 12, 2021*: in the latest version available, incorporating the results of the REMAP-CAP study and of the WHO meta-analysis, sarilumab is considered interchangeable with tocilizumab in the presence of the following criteria:
  <u>*Eligibility criteria*</u>:
  - *COVID-19 infection confirmed by microbiological test o strongly suspected according to the evaluation of a multidisciplinary team* ***AND***
  - *not having received treatment with tociliizumab or sarilumab for the same episode* ***AND***
  - *being treated with dexamethasone or an equivalent corticosteroid, unless contra-indicated* ***AND***
  - ***EITHER***
  - *Hypoxemia with evidence of inflammation but not yet in critical condition requiring respiratory support defined as:*
    - *C-reactive protein level of at least 75 mg/L; AND*
    - *oxygen saturation <92% in ambient air OR need of oxygen supplement;*

- ***Or***
- *In the early stages of critical illness requiring respiratory support (if an IL-6 inhibitor for COVID-19 has not yet been administered) defined as:*
    - *Within 48 hours from initiation of respiratory support (high-flow nasal oxygen, continuous positive airway pressure (CPAP), or non-invasive ventilation or invasive mechanical ventilation), regardless of C-reactive protein level.*

Exclusion criteria and precautions

- *Tocilizumab should not be administered in the following circumstances:*
    - *Known hypersensitivity to tocilizumab*
- *Sarilumab should not be administered in the following circumstances:*
    - *Known hypersensitivity to sarilumab*
    - *A baseline platelet count <150 x 10^9/L*

Caution should be taken when considering treatment with IL-6 inhibitors in the following circumstances:

- *Coexisting infection that may be worsened by IL-6 inhibitor therapy;*
- *Baseline ALT or AST levels higher than 5 times the upper normal limit;*
- *Pre-existing conditions or treatments leading to ongoing immunosuppression.*

Caution is also required when prescribing IL-6 inhibitors to patients with neutropenia or thrombocytopenia.

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