# USE OF SARILUMAB FOR COVID-19 IN HOSPITALISED ADULTS DRUG GUIDELINE

Sarilumab (Kevzara™) is not registered for use in Australia.[1] The National COVID-19 Clinical Evidence Taskforce (current as at 29/09/21) gives a conditional recommendation for use of sarilumab for adults who require high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation.[2] Use in pregnant or breastfeeding women or children and adolescents is NOT recommended outside randomised trials.[2] In the REMAP-CAP trial, sarilumab was found to be equivalent to tocilizumab for improving survival and reducing duration of organ support.[3]

This guideline requires endorsement by your local Drug and Therapeutics Committee (DTC) prior to implementation.

Supply of sarilumab for clinical trials takes precedence over supply for use outside clinical trials.

This guideline aims to provide supportive information for clinicians if they decide to prescribe sarilumab for use in hospitalised patients with COVID-19 when patients are not eligible for a clinical trial or when a clinical trial is not available.[4]

This guideline should be used in conjunction with the Sarilumab resources available here:
- Individual Patient Use (IPU) Application /Prescribing Declaration Form,
- Outcomes Reporting Form,
- Patient Consent Form and/or other consenting information, and
- Patient Information Leaflet.

Access to sarilumab (Kevzara™) is via the *Special Access Scheme (SAS) Category A pathway: notification for a patient defined as seriously ill*.[5] The SAS Category A form (provided with the medication) must be completed and provided to the pharmacy department.

Use of sarilumab is not recommended in the Hospital in the Home setting or in community-based patients with COVID-19.

## Drug Class[6,7]:

Anti-rheumatic, cytokine modulator, interleukin-6 (IL-6) receptor antagonist/inhibitor monoclonal antibody (human).

## Authorised Prescribers:

- Infectious disease physicians,
- Intensivists,
- Respiratory physicians.

Other physicians in accordance with local governance regulations e.g. emergency physicians.

## Indication for applying this guidance[2,8]:

In accordance with relevant DTC approval, sarilumab may be considered for **non**-pregnant/**non**-breastfeeding adults with a current diagnosis of COVID-19:

- who require supplemental high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation AND
- when baricitinib is contraindicated AND
- in preference to tocilizumab*, unless sarilumab is contraindicated (e.g. paediatric patient).

It is recommended to commence sarilumab within 24 hours of commencing supplemental high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation (as per REMAP-CAP).[9]

*If available & not contraindicated, sarilumab is preferred IL-6 inhibitor during tocilizumab shortage.

## Contraindications and Precautions[6,10]:

- **Hypersensitivity**: Contraindicated in patients with known hypersensitivity to sarilumab or any of the excipients of the product, Chinese Hamster Ovary cell products or other recombinant human or humanised antibodies. Exercise caution in patients with a history of anaphylaxis to other medicines.
- **Haematological including Immunosuppression:**
  - Sarilumab may reduce white cell count (WCC) and platelets; do not commence if absolute neutrophil count (ANC) <2 x $10^9$/L and platelets <150 x $10^9$/L.[†]
- **Infection**:
  - Contraindicated in patients with serious active infections (other than COVID-19).
  - Sarilumab treatment is associated with an increased risk of serious infections including bacterial, viral, fungal and opportunistic infections. Use with caution in patients with clinically important risk factors for chronic or recurrent infections.
  - Tuberculosis has been reported in patients receiving sarilumab. Patients should be evaluated for latent tuberculosis.
  - There is an increased risk of serious and sometimes fatal infections when sarilumab is used with other immunosuppressive agents; see section on drug interactions.
  - Patients should be monitored for signs and symptoms of other infections during and after treatment with sarilumab.

    N.B. Baseline testing for HIV, viral hepatitis, strongyloides and tuberculosis should be undertaken. Sarilumab treatment should NOT be delayed pending results of baseline tests.
- **Hepatic**: Exercise caution in patients with active hepatic disease or impairment, including abnormal liver enzymes (ALT or AST greater than 1.5 times the upper limit of normal (ULN)).[†]
- **Gastrointestinal (GI):**
  - GI perforations have been reported. Use with caution in patients at risk of GI perforation. Monitor for new onset abdominal symptoms.
- **Pregnancy and breastfeeding[2]**: Sarilumab is a pregnancy Category C medication. A pregnancy test must be conducted in any COVID-19 positive woman of childbearing age in whom this therapy is being considered. As at 29/9/21, sarilumab is not recommended for use in the treatment of COVID-19 in pregnant or breastfeeding women outside randomised trials with appropriate ethical approval. These recommendations may change as new evidence becomes available. See National COVID-19 Clinical Evidence Taskforce guidelines for further advice regarding management of COVID-19 in pregnant or breastfeeding women.

[†] Please note that exclusion thresholds for REMAP-CAP trial differ to those listed in Product Information of Kevzara®: (baseline platelet count of less than 50 x $10^9$/L, baseline ALT or AST greater than 5 times the ULN.

- **Use in paediatrics[2]:** As at 29/9/21, sarilumab is not recommended for use in the treatment of COVID-19 in children or adolescents outside randomised trials with appropriate ethical approval. These recommendations may change as new evidence becomes available. See National COVID-19 Clinical Evidence Taskforce guidelines for further advice for management.
- **Immunisations:**
  - Live vaccines should not be given concurrently.

## Drug Interactions[11-13]:

Potential drug interactions have not been investigated in patients with COVID-19.

Consider:

- Concurrent use of immunosuppressive/anti-rejection therapy (e.g. infliximab) increases the risk of infection and should be avoided.
- Clozapine: increased risk of agranulocytosis / haematological toxicity.
- Sarilumab has no inhibitory or inducing effects on cytochromes. Sarilumab is expected to normalise cytochrome activity (via inhibition of IL-6) in patients with COVID-19 who experience an elevation of IL-6, which has been shown to suppress activity of drug metabolising enzymes, namely CYP3A4, but also others. This indirect effect of sarilumab on CYP450 enzyme activity may persist for several weeks after administration.
- The indirect effect of sarilumab on CYP450 enzyme activity may be clinically relevant for a CYP450 substrate with a narrow therapeutic index, where the dose is individually adjusted.
  - Caution should be exercised when sarilumab is coadministered with CYP3A4 substrates, especially when reduced effectiveness is undesirable. Specific CYP3A4 substrates that may be co-prescribed include benzodiazepines, opioids, anticoagulants etc.
- The therapeutic effect of recent vaccinations e.g. COVID-19 vaccination may be diminished. Specialist input should be obtained regarding timing of future vaccinations. Concurrent use of live vaccines should be avoided. Information is likely to evolve. Contact the NSW Immunisation Specialist Service (NSWISS) Advice Line (1800 679 477).

A variety of resources are available to check specific drug combinations, e.g. Liverpool COVID-19 Drug Interactions tool and Micromedex drug interaction tool (CIAP link). Contact the local pharmacy department or medicines information service for tailored advice.

## Presentation and storage[6,10]:

- Single use pre-filled injection syringe (PFS) delivering 200 mg per 1.14 mL of sarilumab (175 mg/mL)
- Refrigerate vials at 2–8°C. Do not freeze.

**Note:** The sarilumab (Kevzara®) product is presented as subcutaneous pre-filled syringes (PFS). An intravenous (IV) formulation is not commercially available. Refer to the preparation and administration section for instructions on use of subcutaneous (subcut) formulation for the preparation and administration via intravenous infusion for the treatment of COVID-19.

## Dose[3,8,14,15]:

| Recommended dose is 400 mg as a **single dose via intravenous infusion** over 60 minutes. |
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## Preparation and administration[15-19]:

- The occupational hazard of intermittent low dose exposure to sarilumab is not known. Wear a mask and gloves when preparing the infusion solution to minimise exposure.
- It is recommended that the name and the batch number of the administered product is clearly recorded in order to improve traceability.[10]
- Preferably administer infusion immediately after preparation. If stored at room temperature, the infusion must be used within 4 hours.[16]

| Steps |
|---|
| 1. Add the sarilumab dose (400 mg/2.28 mL) from 2 pre-filled 200 mg syringes (PFS) to the 100 mL sodium chloride 0.9% infusion bag. **Important, see N.B. below**. |
| 2. Invert gently 10 times when mixing to avoid foaming. Do NOT shake. Inspect the bag, which must be clear to opalescent, colourless to pale yellow and free from visible particles. |
| 3. Do not use the same IV line to administer other medications at the same time. |
| 4. Prime the line with sarilumab infusion. Infuse intravenously at an initial slower infusion rate as a precaution for infusion-related reactions: **10 mL per hour for 15 minutes, then increase to 130 mL per hour for at least 45 minutes until the bag is empty** (infusion is given over approximately 60 minutes) via a central or peripheral line.[15] The infusion set must contain a 0.2 micron in-line filter.[18,19] |
| 5. After the sarilumab infusion is completed, run at least 20 mL of sodium chloride 0.9% at 130 mL per hour to flush the giving set (i.e. the same rate as the final sarilumab infusion). |

**N.B. The PFS needle (0.5 inch) may be too short to pierce the internal septum of the sodium chloride 0.9% infusion bag.

Local testing has demonstrated that:

a) the Fresenius Kabi Sodium Chloride 0.9% Freeflex® 100 mL bag allows the full dose of sarilumab to be injected into the additive port from the PFS.[18,19]

b) the 0.5 inch PFS needle may not pierce the internal septum within the additive port of Baxter sodium chloride 100mL bags. No information regarding the utility of other brands of sodium chloride 0.9% is known.

If Fresenius Kabi Sodium Chloride 0.9% Freeflex® bags are not available, consider:

a) use of an IN-Stopper: attach a 21 gauge BD needle to a B Braun IN-Stopper® and insert this into the additive port of the saline bag (https://www.bbraun.com.au/en/products/b/in-stopper.html); then inject the contents of the PFS through the membrane of the IN-Stopper; flush the membrane with approximate 0.5 mL of air to ensure the 0.2 mL priming volume has been added to the bag.

b) pre-piercing the injection port septum first prior to injecting the contents of the PFS. Flush the port with 5 mL of saline or 0.5 mL of air after using the PFS to assist flushing of any sarilumab stuck in the port.[18] (Least preferred method).

## Monitoring Requirements[6,10,15]:

- Monitor for adverse effects (as below) – including FBC (specifically neutrophils and platelets), LFTs (transaminases and bilirubin).
- Monitor C-Reactive Protein (CRP) levels following administration of sarilumab.
- Observe for hypersensitivity reaction during and for 30 minutes after the IV infusion. Resuscitation facilities must be readily available.

## Adverse Effects[¥]:

It may be difficult to distinguish between adverse effects of sarilumab and signs and symptoms of COVID-19. As sarilumab is not registered in Australia, it is important to document and report all (from possible to confirmed) adverse effects experienced by the patient during treatment to inform its safety profile and future use. ¥ Refer to product information for complete list of possible adverse effects[6,10].

- **Common (>1%):** Infections (including opportunistic), neutropenia, thrombocytopenia, leukopenia, injection site reactions (e.g. erythema and pruritus), increased liver enzymes, increased serum cholesterol and triglycerides, headache, diarrhoea.
- **Infrequent (0.1–1%):** GI perforation, hypersensitivity reactions (e.g. urticaria, angioedema).
- **Rare (<0.1%):** Malignancy.

## Reporting:

Access via the IPU/Prescribing Declaration pathway will enable appropriate medicines governance and ensure the collection and analysis of patient outcomes and systematic monitoring of medicines use. An outcomes reporting process will be forthcoming. The prescribing clinician is responsible for reporting medication errors and adverse events occurring as a result of sarilumab treatment:

- Adverse events related to medicines should be reported to the TGA and via the hospital ims+ or Riskman system.
- Approval of sarilumab IPU should be accompanied with reporting of clinical outcomes. Prescribing declarations or IPU applications and outcome reporting should occur as per local governance processes. A NSW TAG-developed drug registry using online Prescribing Declaration or IPU application and outcome reporting processes has been developed. See https://www.nswtag.org.au/covid-19-medicines-resources/. Contact your local DTC or pharmacist for further information.

## Summary of amendments/updates made in version 1.1 11 October 2021:

- Preparation & administration section (page 4): added several options to overcome the pre-filled syringe needle being too short to pierce the internal septum of some brands of sodium chloride 0.9% infusion bags; added use of in-line filter
- Throughout: updated to reflect current National COVID-19 Clinical Evidence Taskforce guideline date.

## References:


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