DRUG GUIDELINE
Use of sarilumab injection for COVID-19

Introduction[1-4]

Sarilumab (Kevzara™) is not registered for use in Australia. The National COVID-19 Clinical Evidence Taskforce gives a conditional recommendation to consider use of sarilumab for the treatment of COVID-19 in adults who require high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation.

Sarilumab is not an alternative or substitute for vaccination. **Vaccination is the preferred and primary option for the prevention of COVID-19.**

This guideline requires endorsement by your local Drug and Therapeutics Committee (DTC) prior to implementation. Additional resources to support the safe and appropriate use of sarilumab are available here.

Access to sarilumab (Kevzara™) is via the *Special Access Scheme (SAS) Category A pathway: notification for a patient defined as seriously ill*. The SAS Category A form must be completed and provided to the Pharmacy Department prior to receiving supply. Contact your pharmacy department if assistance is required.

Drug class and mechanism of action[5-7]

In severe disease states, an overactive immune response can result in increased production of cytokines, such as interleukin-6, exacerbating inflammation and delaying recovery. Sarilumab is a recombinant humanised monoclonal antibody which binds to the receptors of the cytokine interleukin-6, reducing inflammation and improving ability to recover from SARS-CoV-2 virus.

Indication[2, 7-10]

Sarilumab may be considered for **non-pregnant and non- breastfeeding adults** with a current diagnosis of COVID-19:

- who require supplemental high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation

  AND

- baricitinib OR tocilizumab are unavailable or contraindicated.

It is recommended to commence sarilumab within 24 hours of commencing supplemental high- flow oxygen, non-invasive ventilation or invasive mechanical ventilation.

In the REMAP-CAP trial, sarilumab and tocilizumab were found to equally improve survival rates and reduce duration of organ support for COVID-19 patients. However, data regarding sarilumab is less robust than for tocilizumab. Tocilizumab should be used in preference to sarilumab.

Contraindications and precautions[5-6]

- Patients with a history of any reaction consistent with hypersensitivity to any component of the product, Chinese hamster ovary cell products or other recombinant human or humanised antibodies.
- Patients with sepsis or active, severe infections from non-COVID-19 pathogens.
- Use with caution in patients with a history of anaphylaxis to other medicines.
- Patients using sarilumab may be susceptible to serious and fatal opportunistic infections, reactivation of latent tuberculosis, viruses, and fungal infections. Use with caution if patient has a history of recurring or chronic

infection, or underlying conditions (e.g. diabetes) which may predispose them to infections. Baseline testing for HIV, viral hepatitis, strongyloides and tuberculosis should be undertaken.
- Avoid concurrent immunosuppressive/anti-rejection therapy to reduce risk of serious infections.
- Use with caution in patients at increased risk of gastrointestinal perforation. Patients presenting with symptoms potentially indicating gastrointestinal perforation or diverticulitis should be evaluated promptly.
- Sarilumab therapy should not be initiated if transaminases ALT or AST > 1.5 times upper limit of normal (ULN), platelets < 150 x 10^9/L or absolute neutrophil count (ANC) < 2 x 10^9/L.
- Live vaccinations should not be given concomitantly.
- See *Pregnancy, breastfeeding and contraception* section for recommendations in pregnancy, breastfeeding and contraception.

Pregnancy, breastfeeding and contraception[2,5-6]

The National COVID-19 Clinical Evidence Taskforce guidelines do not recommend sarilumab use in pregnancy and breastfeeding for treatment of COVID-19, outside randomised trials with appropriate ethical approval. The use of any medicine during pregnancy and breastfeeding requires careful consideration of both risks and benefits by treating health professionals.

Pregnancy
Sarilumab has been classified as **pregnancy category C** by the Therapeutic Goods Administration.

Breastfeeding
There is no established safety data for use in pregnancy and it is not known if sarilumab passes into breast milk.

Contraception

Women of childbearing potential must use effective contraception during and up to 3 months after treatment. The effectiveness of oral contraceptives may be reduced due to sarilumab use. Consider use of barrier or other contraceptives.

Drug interactions[5-6,11-13]

Potential drug interactions have not been investigated in patients with COVID-19. Resources such as the Liverpool COVID-19 drug interactions tool and Micromedex drug interactions tool may be useful to check for specific drug-drug interactions. Generally:

- Concurrent use of sarilumab with immunosuppressive/anti-rejection therapy may increase risk of infection.
- The cytokine interleukin-6 suppresses expression of the drug metabolising enzymes (cytochromes) CYP450, CYP3A4 and to a lesser extent, CYP1A2, CYP2C9 and CYP2C19. Sarilumab inhibits interleukin-6, potentially reversing its suppressing impact on cytochrome expression for several weeks after stopping therapy.
- Drugs metabolised via the above cytochromes should be monitored as doses may need to be adjusted to maintain therapeutic effect, particularly if they have a narrow therapeutic index e.g. warfarin, theophylline.
- There may be a reduction in exposure and expression of CYP3A4 substrates if sarilumab is co-administered. e.g statins and the oral contraceptive pill may not be as effective.
- Live and live-attenuated vaccines should not be given concurrently as clinical safety has not been established. Contact the NSW Immunisation Specialist Service (NSWISS) Advice Line for further advice.

Presentation, storage and stability[10,14]

- Sarilumab is available as a single use pre-filled injection syringe (PFS) delivering 200 mg per 1.14 mL of sarilumab (175 mg/mL).
- Refrigerate at 2–8°C. Do not freeze.
- Preferably administer infusion immediately after preparation. If it will be administered later, ensure the prepared solution is appropriately labelled, stored at room temperature and used within 4 hours.

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

Dose and route of administration[9,15-16]

The recommended dose for adults is 400 mg as a single dose via intravenous infusion over 60 minutes.

Preparation and administration[15,17-19]

Preparation of vials

The occupational hazard of intermittent low dose exposure to sarilumab is not known. To minimise exposure, gloves and surgical mask should be worn when preparing this medication. Please refer to local protocol or guidelines on this matter.

Dilution^

1. Using aseptic technique, add the sarilumab dose (400 mg/2.28 mL) from 2 pre-filled 200 mg syringes to a 100 mL sodium chloride 0.9% infusion bag^.
2. To mix the solution, gently invert the bag to avoid foaming. Do NOT shake.
3. Inspect the bag to make sure it is clear to opalescent, colourless to pale yellow and free from visible particles, prior to administration.

Administration#

Infuse intravenously over 60 minutes via a dedicated IV line. Do not use the same IV line to administer other medications at the same time#. The infusion set must contain a 0.2 micron in-line filter.[18,19]

^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:

- 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.
- 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:

- 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 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.
- pre-piercing the injection port septum first prior to injecting the contents of the PFS. Flush the port with 5 mL of sodium chloride 0.9% or 0.5 mL of air after using the PFS to assist flushing of any sarilumab stuck in the port (least preferred method).

An initial slower infusion rate may be used to reduce the potential for infusion-related reactions. The NHS recommends 10 mL/hour for first 15 minutes then 130 mL/hour for the remaining 45 minutes, followed by a 20 mL sodium chloride 0.9% flush.

Monitoring requirements[5-6,14]

- Observe for hypersensitivity reaction during, and for 30 minutes after IV infusion.
- Monitor for infusion related reactions, changes to neutrophils, platelets or transaminases warranting intervention and adverse effects including signs of new infection or reactivation of latent conditions, gastrointestinal symptoms suggestive of perforation or diverticulitis.

Adverse effects[5-6,9]

It may be difficult to distinguish between adverse effects of sarilumab and signs and symptoms of COVID-19. As the proposed use is off-label, 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 the Product Information for complete list of possible adverse effects.

- **Common (≥ 1% to < 10%):** Infections (including opportunistic), neutropenia, thrombocytopenia, leukopenia, injection site reactions (e.g. erythema and pruritus), increased liver enzymes, increased serum cholesterol and triglycerides, antibody development, nasopharyngitis.
- **Infrequent (0.1 – < 1%):** GI perforation, hypersensitivity reactions (e.g. urticaria, angioedema).

Reporting

- Suspected adverse events should be reported to the TGA, Sanofi-Aventis (drug sponsor) and through the local incident reporting system. As sarilumab is not registered for use in Australia, it is important to document and report all suspected adverse effects experienced by the patient during treatment to inform its long-term safety profile and future use.
- Drug and Therapeutics Committee oversight in the access process will enable appropriate medicines governance and ensure the collection and analysis of patient outcomes and systematic monitoring of medicine use. Sarilumab use and outcome reporting should occur as per local governance processes.

Summary of major changes made in version 1.4 – March 2022

- Changed recommendation to only use sarilumab if baricitinib or tocilizumab are unavailable or contraindicated.
- Data from REMAP-CAP trial included in indication section.
- Dedicated section for pregnancy, breastfeeding and contraception information.
- Removed monitoring for CRP. Added monitoring for infection and GI symptoms.
- Removed adverse effects of headache, diarrhoea and malignancy. Added nasopharyngitis and antibody development.
- General formatting changes and rewording/condensing of information (without loss of content).

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