

**COVID-19 Tocilizumab & Sarilumab**  
**Treatment Protocol**

**COVID DOCUMENT**

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| <b>CLASSIFICATION:</b>  | Clinical  |
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| <ul style="list-style-type: none"><li>• <b>Recommended Reading for:</b></li></ul> | Clinicians, All non-medical Prescribers, Pharmacists and Nurses |
| <ul style="list-style-type: none"><li>• <b>Information for:</b></li></ul>         | Ward Managers, Senior Nurses, ADNs, Divisional Directors        |

# **COVID-19 Tocilizumab & Sarilumab**

## **Treatment Protocol**

Tocilizumab and sarilumab are recombinant humanised monoclonal antibodies that block the interleukin-6 (IL-6) receptor, potentially mitigating the IL-6 mediated systemic and local effects seen within COVID-19. The REMAP-CAP trial has reported with tocilizumab or sarilumab an overall reduction in risk of death of 24% in patients and reduced the time patients spent in the ICU by more than a week on average. The RECOVERY trial has reported on tocilizumab that use in a broad hospitalized population setting that it significantly improved survival and other clinical outcomes in patients with hypoxaemia and systemic inflammation.

A rapid evidence review published by the National Institute for Health and Care Excellence (NICE) on 20 January 2021 suggested that any mortality or recovery benefit from sarilumab is seen only in the most severely ill patients given sarilumab soon after organ support is started, when any developing organ dysfunction may be more reversible.

### **Criteria for use of Tocilizumab & Sarilumab in patients with COVID-19**

We recommend that the use of tocilizumab & sarilumab should be considered after the consultant's ward round when patient's eligibility for the treatment and the potential risks of use of the medication are considered.

Patients must meet all the following criteria and none of the exclusion criteria as outlined below. This is reflected in the NHSE Blueteq criteria that must be completed for each patient who receives treatment.

See [appendix 1](#) for how to initiate.

### **Eligibility criteria for Tocilizumab (all must be met):**

- Being an in-patient
- Age older than 18
- Tested positive for SARS-CoV-2 infection or MDT has high level of confidence that COVID-19 most likely diagnosis
- Already on dexamethasone for COVID-19
- Oxygen saturation < 92% on room air or requiring oxygen supplementation
- CRP of equal to or greater than 75 mg/L

### **Exclusion criteria for Tocilizumab (none must be present):**

- Having received an IL-6 inhibitor in this admission
- Known hypersensitivity to tocilizumab or sarilumab
- Serum ALT or AST greater than five times of the upper limit of normal (ALT: greater than 270 U/L, AST: greater than 170 U/L)
- Co-existing infection that might be worsened by tocilizumab\* (see under sarilumab exclusion criteria).
- Neutrophil count <  $2 \times 10^9/L$
- Platelet count <  $50 \times 10^9/L$

Discuss with Respiratory, or ID consultants when required.

### **Eligibility criteria for Sarilumab (all must be met):**

- Being an in-patient
- Age older than 18
- Confirmed COVID-19 test or MDT has high level of confidence that COVID-19 most likely diagnosis
- Treated <24 hours with respiratory support (high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation
- Patients should be treated as early as possible in their critical illness, ideally <24 hours since commencing respiratory support (as defined above). Treatment can be started within 48 hours of starting respiratory support for relevant clinical reasons e.g. transfer of patients.

### **Exclusion criteria for Sarilumab (none must be present):**

- Known hypersensitivity to sarilumab
- Having received an IL-6 inhibitor in this admission
- Co-existing infection that might be worsened by sarilumab\*.
- Baseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than 5 times the upper limit of normal (caution is recommended if hepatic enzymes are more than 1.5 times the upper limit of normal)
- Baseline platelet count of <150 x 10<sup>9</sup>/L
- Baseline absolute neutrophil count of <2 x 10<sup>9</sup>/L
- Pre-existing condition or treatment resulting in ongoing immunosuppression

*\*Any active, severe infection other than COVID-19; caution is advised when considering the use of tocilizumab or sarilumab in patients with a history of recurring or chronic infections or with underlying conditions which may predispose patients to infections.*

### **Pregnancy and breast feeding**

Data on the use of tocilizumab & sarilumab during pregnancy is scant. The potential risk to human foetus is unknown.

The use of tocilizumab in pregnancy is not recommended unless clearly necessary. In those cases, clear documentation of a discussion on the risks to the foetus with the patient and their partner is advised. There are currently no data on the risk to infants through breast milk. Breast feeding women requiring tocilizumab & sarilumab must be advised to formula feed their babies for seven weeks after the dose of tocilizumab.

Sarilimumab SPC currently states women of childbearing potential should use effective contraception during and up to 3 months after treatment. There are no or limited amount of data from the use of sarilumab in pregnant women.

### Dose of Tocilizumab for COVID-19 patients:

The recommended dose is 8 mg/kg (see dosing table below) administered intravenously with 0.9% sodium chloride over one hour and as a single dose. The total dose of tocilizumab must not exceed 800 mg

| Weight          | Dose of Tocilizumab            |
|-----------------|--------------------------------|
| <41kg           | 8mg/kg rounded to nearest 20mg |
| ≥41kg and ≤45kg | 360mg                          |
| ≥46kg and ≤55kg | 400mg                          |
| ≥56kg and ≤65kg | 480mg                          |
| ≥66kg and ≤80kg | 600mg                          |
| ≥81kg and ≤90kg | 680mg                          |
| ≥91kg           | 800mg                          |

### Dose of Sarilumab for COVID-19 patients:

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

### Administration of Tocilizumab for COVID-19 patients:

- See [appendix 2](#) for how to prepare tocilizumab for administration

### Administration of Sarilumab for COVID-19 patients:

- See [appendix 3](#) for how to prepare sarilumab for administration

### Co-administration:

There is no significant interaction between dexamethasone or hydrocortisone and tocilizumab or sarilumab. Please use the University of Liverpool COVID-19 Drug Interactions Website for more information: <https://www.covid19-druginteractions.org/checker>

### Side effects:

Neither tocilizumab or sarilumab are licenced for use in patients with COVID-19. Please ensure that adverse reactions are reported via the dedicated yellow card reporting site: <https://coronavirus-yellowcard.mhra.gov.uk/>.

### Safety considerations:

Tocilizumab and sarilumab can cause immunosuppression that renders patients at risk of bacterial and fungal infections. Low clinical threshold for identification and management of infection must be used.

**Monitoring:**

Patients must be regularly clinically assessed for bacterial infection. A blood culture must be obtained for all patients with fever and where treatment for bacterial infection is commenced. Discuss with ID and microbiology consultants when required.

All patients receiving tocilizumab and sarilumab must be tested for HIV, Hepatitis B, and Hepatitis C infections. Please request HIV antibody, hepatitis B surface antigen, hepatitis B core antibody and Hepatitis C antibody tests. Please discuss the results with microbiology or ID physicians if unsure on how to interpret the results.

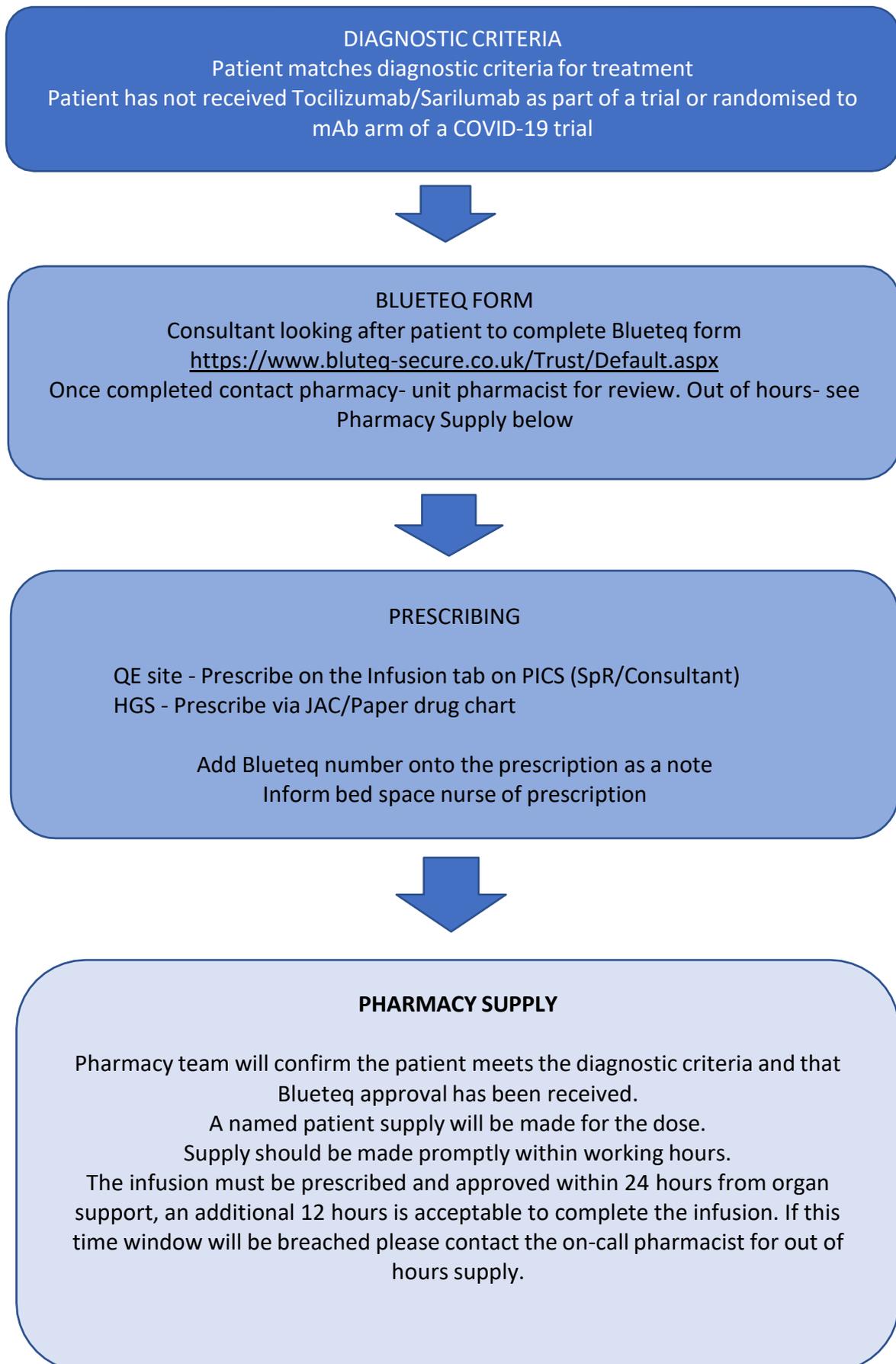
All patients must have neutrophil, platelet and LFT's monitored at baseline and after infusion.

**At discharge:**

- Tocilizumab and sarilumab are immunosuppressants which can suppress CRP response for up to 3 months after administration
- The discharge summary should state that tocilizumab or sarilumab were given and the date administered
- The GP should have a low threshold for giving antibiotics or readmitting if the patient becomes unwell with suspected sepsis during three months following discharge

## Appendix 1.

### INITIATING TOCILIZUMAB / SARILUMAB FLOWCHART



## Appendix 2.

### TOCILIZUMAB DRUG PREPARATION AND ADMINISTRATION GUIDANCE

| <b>To be prepared by suitably trained nursing staff</b>   |  |        |                       |  |           |         |  |        |  |        |  |        |   |       |  |        |       |       |        |       |       |        |       |       |        |       |   |        |
|---|--|--------|-----------------------|--|-----------|---------|--|--------|--|--------|--|--------|---|-------|--|--------|-------|-------|--------|-------|-------|--------|-------|-------|--------|-------|---|--------|
| <p>This method uses Tocilizumab vials (RoActemra)</p> <p>Tocilizumab dose = ..... mg (check it fits the dosebanding table to the right)</p> <p>Volume of tocilizumab 20mg/mL concentrate required =</p> <p>Dose of tocilizumab (mg) ÷ 20 (mg/mL)</p> <p>= _____ mg ÷ 20 (mg/mL) = _____ mL</p>  | <table border="1"> <thead> <tr> <th colspan="2">Patient Body Weight *</th> <th rowspan="2">Band Dose</th> </tr> <tr> <th>From ≥</th> <th>To ≤</th> </tr> </thead> <tbody> <tr> <td>-</td> <td>40 kg</td> <td></td> </tr> <tr> <td>41 kg</td> <td>45 kg</td> <td>360 mg</td> </tr> <tr> <td>46 kg</td> <td>55 kg</td> <td>400 mg</td> </tr> <tr> <td>56 kg</td> <td>65 kg</td> <td>480 mg</td> </tr> <tr> <td>66 kg</td> <td>80 kg</td> <td>600 mg</td> </tr> <tr> <td>81 kg</td> <td>90 kg</td> <td>680 mg</td> </tr> <tr> <td>91 kg</td> <td>-</td> <td>800 mg</td> </tr> </tbody> </table> |        | Patient Body Weight * |  | Band Dose | From ≥  | To ≤                                     | -      | 40 kg                                      |        | 41 kg                                      | 45 kg  | 360 mg                                  | 46 kg | 55 kg  | 400 mg | 56 kg | 65 kg | 480 mg | 66 kg | 80 kg | 600 mg | 81 kg | 90 kg | 680 mg | 91 kg | - | 800 mg |
|   | Patient Body Weight *  |        | Band Dose             |  |           |         |  |        |  |        |  |        |   |       |  |        |       |       |        |       |       |        |       |       |        |       |   |        |
| From ≥  | To ≤   |        |                       |  |           |         |  |        |  |        |  |        |   |       |  |        |       |       |        |       |       |        |       |       |        |       |   |        |
| -   | 40 kg  |        |                       |  |           |         |  |        |  |        |  |        |   |       |  |        |       |       |        |       |       |        |       |       |        |       |   |        |
| 41 kg   | 45 kg  | 360 mg |                       |  |           |         |  |        |  |        |  |        |   |       |  |        |       |       |        |       |       |        |       |       |        |       |   |        |
| 46 kg   | 55 kg  | 400 mg |                       |  |           |         |  |        |  |        |  |        |   |       |  |        |       |       |        |       |       |        |       |       |        |       |   |        |
| 56 kg   | 65 kg  | 480 mg |                       |  |           |         |  |        |  |        |  |        |   |       |  |        |       |       |        |       |       |        |       |       |        |       |   |        |
| 66 kg   | 80 kg  | 600 mg |                       |  |           |         |  |        |  |        |  |        |   |       |  |        |       |       |        |       |       |        |       |       |        |       |   |        |
| 81 kg   | 90 kg  | 680 mg |                       |  |           |         |  |        |  |        |  |        |   |       |  |        |       |       |        |       |       |        |       |       |        |       |   |        |
| 91 kg   | -  | 800 mg |                       |  |           |         |  |        |  |        |  |        |   |       |  |        |       |       |        |       |       |        |       |       |        |       |   |        |
| <table border="1"> <thead> <tr> <th colspan="2">Materials Required</th> </tr> <tr> <th>Medicine</th> <th>Storage</th> </tr> </thead> <tbody> <tr> <td>Tocilizumab 80mg in 4mL vial (RoActemra)</td> <td>Fridge</td> </tr> <tr> <td>Tocilizumab 200mg in 10mL vial (RoActemra)</td> <td>Fridge</td> </tr> <tr> <td>Tocilizumab 400mg in 20ml vial (RoActemra)</td> <td>Fridge</td> </tr> <tr> <td>Sodium Chloride 0.9% 100mL Infusion Bag</td> <td>Fluid</td> </tr> <tr> <td colspan="2"><i>Record batch details in PICS/on JAC/ on Paper Chart</i></td> </tr> </tbody> </table> |  |        | Materials Required    |  | Medicine  | Storage | Tocilizumab 80mg in 4mL vial (RoActemra) | Fridge | Tocilizumab 200mg in 10mL vial (RoActemra) | Fridge | Tocilizumab 400mg in 20ml vial (RoActemra) | Fridge | Sodium Chloride 0.9% 100mL Infusion Bag | Fluid | <i>Record batch details in PICS/on JAC/ on Paper Chart</i> |        |       |       |        |       |       |        |       |       |        |       |   |        |
| Materials Required  |  |        |                       |  |           |         |  |        |  |        |  |        |   |       |  |        |       |       |        |       |       |        |       |       |        |       |   |        |
| Medicine  | Storage  |        |                       |  |           |         |  |        |  |        |  |        |   |       |  |        |       |       |        |       |       |        |       |       |        |       |   |        |
| Tocilizumab 80mg in 4mL vial (RoActemra)  | Fridge   |        |                       |  |           |         |  |        |  |        |  |        |   |       |  |        |       |       |        |       |       |        |       |       |        |       |   |        |
| Tocilizumab 200mg in 10mL vial (RoActemra)  | Fridge   |        |                       |  |           |         |  |        |  |        |  |        |   |       |  |        |       |       |        |       |       |        |       |       |        |       |   |        |
| Tocilizumab 400mg in 20ml vial (RoActemra)  | Fridge   |        |                       |  |           |         |  |        |  |        |  |        |   |       |  |        |       |       |        |       |       |        |       |       |        |       |   |        |
| Sodium Chloride 0.9% 100mL Infusion Bag   | Fluid  |        |                       |  |           |         |  |        |  |        |  |        |   |       |  |        |       |       |        |       |       |        |       |       |        |       |   |        |
| <i>Record batch details in PICS/on JAC/ on Paper Chart</i>  |  |        |                       |  |           |         |  |        |  |        |  |        |   |       |  |        |       |       |        |       |       |        |       |       |        |       |   |        |

#### 1. Preparation, administration and disposal of intravenous tocilizumab infusion

In addition to the information provided in the table below, please follow the general principles of preparing injectable medicines in a clinical area.

1. Ensure the preparation area is clean and clear. Collect the appropriate number of tocilizumab vials from the fridge and a 100mL IV infusion of sodium chloride 0.9%.
2. Ensure the appropriate personal protective equipment (PPE) is worn as per Critical Care guidance. However, this must include gloves, an apron, an FFP3 face mask and goggles (or a visor).
3. Tocilizumab solutions should be clear to opalescent, colourless to pale yellow and free of visible particles, in order to be deemed suitable for administration.
4. Using an appropriate volume IV syringe, withdraw XmL of sodium chloride 0.9% from the 100mL sodium chloride 0.9% IV infusion.  
(XmL is the volume of tocilizumab calculated as required for the patient's dose. E.g. if a dose of 800mg (40mL) of tocilizumab 20mg/ml solution is prescribed, then remove 40mL of sodium chloride 0.9% from the 100ml infusion).
5. Discard the withdrawn sodium chloride 0.9% inside the syringe and needle into a yellow sharps bin.
6. Using an appropriate volume IV syringe, draw up XmL of tocilizumab 20mg/mL solution required for the prescribed dose from the vial(s), as calculated above.  
(XmL is the volume of tocilizumab 20mg/ml required, as calculated for the patient's dose. E.g. if 800mg Tocilizumab is prescribed, 40mL of tocilizumab 20mg/ml is needed)
7. **SLOWLY** add the tocilizumab solution to the sodium chloride 0.9% IV infusion to make a final volume of 100mL.
8. Dispose of the tocilizumab needle and syringe in a sharps bin

|  |
|--|
| 9. Mix the tocilizumab solution by gently inverting several times to avoid foaming. <b>DO NOT SHAKE THE SOLUTION - THIS WILL CAUSE THE SOLUTION TO FOAM AND YOU WILL NOT BE ABLE TO USE IT.</b>  |
| 10. Complete and apply an IV infusion label to the tocilizumab IV infusion.  |
| 11. Obtain a second check for the IV tocilizumab infusion from a colleague and sign for preparation and administration on PICS   |
| 12. Record baseline observations for the patient before starting the infusion – heart rate, BP, temperature, respiratory rate.   |
| 13. Connect the tocilizumab IV infusion to the patient IV line and administer over 1 hour via a volumetric infusion pump. Do not infuse any other medicines via the same IV line whilst the tocilizumab is being administered.   |
| 14. Complete patient observations and monitor the patient for signs of hypersensitivity to tocilizumab as follows: 15 minutes after starting the infusion, then every 30 minutes during the infusion and for 1 hour after the end of infusion.<br>Monitoring time points after starting the infusion: 15mins, 45mins, 1hour 15mins, 1 hour 45mins.   |
| 15. Acute infusion reactions can occur during the administration of tocilizumab or within 24hours of infusion.<br>For mild reactions such as flushing and chills, the infusion rate can be slowed down and the patient continually monitored. Notify the doctors of the patient reaction.<br>For severe reactions such as hives, difficulty breathing, chest pain, high or low blood pressure, swelling of face and hands, fever, chills or anaphylaxis or when mild reactions persist despite slowing the infusion, <b>stop the infusion and inform the doctors immediately for additional treatment.</b> |
| 16. Once the tocilizumab infusion is complete, take down the infusion and flush the giving set with 20mL of sodium chloride 0.9% over 15 minutes to ensure all the tocilizumab has been given.   |
| 17. Dispose of the infusion and giving set in a sharps bin.  |

## Appendix 3 .

### SARILUMAB DRUG PREPARATION AND ADMINISTRATION GUIDANCE

#### Dosage

Single dose of 400 mg given via intravenous infusion over 60 minutes.

| Materials required - (record batch details on PICS / drug chart) |         |          |
|--|---------|----------|
| Medicine   | Storage | Quantity |
| Sarilumab 200mg/1.14ml prefilled syringe (Kevzara)               | Fridge  | 2        |
| Sodium chloride 0.9% 100ml infusion bag                          | Fluid   | 1        |

#### Preparation, Administration & Disposal

In addition to the information provided in the table below, please follow the general principles of preparing injectable medicines in a clinical area.

|  |
|--|
| 1. Wear personal protective equipment (PPE), i.e. gown, gloves, protective eyewear and respirator mask.  |
| 2. Prepare in a well-ventilated area in clean utility drug preparation room.   |
| 3. Obtain two 200 mg pre-filled sarilumab syringes (200 mg/1.14ml) to make a 400 mg dose.  |
| 4. Allow syringes to reach room temperature (stored in fridge).  |
| 5. Inject the contents of two syringes into a 100 ml bag of sodium chloride 0.9%. Note: The needle attached to the sarilumab syringe is approx. ½" (12.5mm) long. Take care to ensure it fully penetrates the port and reaches the fluid.                        |
| 6. Invert bag 10 times to mix ( <b>do not shake</b> ).   |
| 7. Ensure the product solution is clear and free from any precipitation. Label as per local policy   |
| 8. Can be administered via a central or peripheral line.   |
| 9. Do not infuse concomitantly in the same IV line with other medications.   |
| 10. Use infusion immediately. If not possible, infusion may be started within a maximum of 4 hours after preparation.  |
| 11. Infuse over 60 minutes (10 ml per hour for 15 minutes, then 130 ml per hour for remaining 45 minutes) using a 0.2micron filter.  |
| 12. Monitor for infusion related reactions: Chills, nausea, headache, wheezing, itching, flushing, pyrexia, dizziness. If infusion related reactions are mild, stop infusion and treat symptoms. Reduce infusion rate by at least 50% when re-starting infusion. |
| 13. For severe infusion related reaction, <b>stop the infusion and inform the doctor immediately to treat the symptoms</b>   |
| 14. Once the sarilumab infusion is complete, take down the infusion and flush the giving set with 20mL of sodium chloride 0.9% at same rate as infusion.   |
| 15. Document administration including batch numbers in clinical noting.  |
| 16. Dispose of the infusion and giving set in a sharps bin   |