Sarilumab (Kevzara) 200mg in 1.14mL (175mg/mL) Pre-filled Syringes Drug Protocol and Guideline for use in Critically ill Adult Patients with COVID-19 Pneumonia

Background

The Department of Health and Social Care issued an updated rapid policy statement on 17 February 2021 regarding the commissioning position for the use of tocilizumab for critically ill patients with COVID-19 pneumonia in adults.

This was supported by a COVID 19 Therapeutic Alert recommending that two Interleukin-6 (IL-6) inhibitors – tocilizumab and sarilumab – are made available as a treatment option for critically ill adult patients hospitalised with COVID-19 in accordance with the agreed criteria.

This document is intended to support the use and describe the governance arrangements for use of sarilumab **via the intravenous route** within CDDFT.

Sarilumab (Kevzara®) It is a human monoclonal antibody that specifically binds to interleukin-6 receptors and blocks the activity of pro-inflammatory cytokines. Sarilumab for subcutaneous use has a marketing authorisation for adults with moderate to severe rheumatoid arthritis. **The use of sarilumab in COVID-19 is off-label (both indication and route of administration) but supported by national guidance and CDDFT clinical standards and therapeutics committee (CSTC).**

A rapid evidence review published by NICE on 20 January 2021 suggested that mortality and recovery benefit from sarilumab is only seen in the most severely ill patients given sarlilumab soon after respiratory support is started and when any developing organ dysfunction may be more reversible

Indication for Use

In ITU settings

Within an ITU setting the decision to prescribe must be made after discussions between TWO ITU consultants. Sarilumab will be stocked on ITU and staff must follow ITU processes to ensure reconciliation.

In approved areas outside of ITU

At present Sarilumab must not be used outside ITU areas.

Eligibility Criteria

Must meet **all** of the following eligibility criteria and none of the exclusion criteria. Hospitalised patients are eligible to be considered for sarilumab if:

- COVID-19 infection is confirmed (either by microbiological testing or where a multidisciplinary team has a high level of confidence that the clinical and radiological features suggest that COVID-19 is the most likely diagnosis).
- Treated with respiratory support (high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation

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- Treatment can be initiated within 24 hours of commencement of respiratory support.
  - This can be extended up to a maximum of 48 hours. However, the principle is to treat patients as early as possible in their critical illness.
- The decision to prescribe has been confirmed with both a respiratory consultant and an ITU consultant.
- The patient has been be deemed suitable for escalation for critical care.
- Has none of the exclusion criteria.

Exclusion Criteria
Any of the following features exclude the patient from the use of sarilumab.
- More than 48 hours after starting respiratory support.
- A 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).
- A pre-existing condition or treatment resulting in ongoing immunosuppression.
- A baseline platelet count of less than 150 x 10^9 /L
- Co-existing infection that might be worsened by sarilumab.
  - Any active, severe infection other than COVID-19; caution is advised when considering the use of sarilumab in patients with a history of recurring or chronic infections or with underlying conditions which may predispose patients to infections.
- Known hypersensitivity to sarilumab.

Presentation

A solution in concentration of 175mg per mL available as:
- Sarilumab 200mg in 1.14mL pre-filled syringes
- Pre-filled syringes should be stored in a refrigerator (2°C–8°C). Do not freeze.

Note this is an off-licence indication and route of administration.
Other preparations of Sarilumab are available but should not be used in the treatment of COVID-19.

Dose and Method of Administration

Dose - ONE single 400mg dose

Route - Intravenous infusion

Instructions for Dilution
Full monograph available via Medusa IV Drug Guide
Allow TWO x 200mg pre-filled sarilumab syringes to reach room temperature.
- Inject the contents of the TWO syringes into a 100mL sodium chloride 0.9% infusion bag.
- Invert bag at least 10 times to ensure thorough mixing
- Make sure the bag is appropriately labelled as per Trust policy.
- It must be administered with an infusion set including a low protein-binding 0.2 micron (or equivalent) filter via a volumetric pump

- It should not be infused concomitantly in the same intravenous line with other drugs.
- Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted.

Administration
- The diluted solution MUST be given as an intravenous infusion.
- Start the infusion at 10mL per hour for the first 15 minutes then 130mL per hour for the subsequent 45 minutes.
- Total infusion time 60 minutes
- This should be followed by a 20mL Sodium Chloride 0.9% flush administered at the same rate the infusion was given.

Special Populations

Caution is advised and a discussion of the risk / benefit should be undertaken before using sarilumab in patients with the following characteristics:
- A baseline absolute neutrophil count of less than 2 x 10^9 /L

Use in Breastfeeding
The SmPC states that it is unknown whether sarilumab is excreted in human breast milk. *IgG1 are excreted in human milk, a decision should be made whether to discontinue breast-feeding or to discontinue sarilumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman*

Use in pregnant patients or women of childbearing potential
Sarilumab should not be used during pregnancy unless clinically necessary.
The SmPC states that women of childbearing potential should use effective contraception during and up to THREE months after treatment

More information is available in the Summary of Product Characteristics (SmPC) for sarilumab

Co-Administration with Other COVID Therapies

Corticosteroids
Administration of systemic dexamethasone or hydrocortisone is recommended in the management of patients with severe or critical COVID-19 infection.
Sarilumab should not be regarded as an alternative to corticosteroids.

Remdesivir
There is also a Clinical Commissioning Policy for the use of remdesivir in hospitalised patients with COVID-19 infection who require supplemental oxygen. There is no interaction of sarilumab with remdesivir expected.

For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

Monitoring and Adverse Drug Reactions

Monitoring

- Check Full blood count (FBC), Liver Function Tests (LFTs), Urea & Electrolytes (U&Es)
- Check Temperature, Heart Rate (HR), Respiratory Rate (RR) and Blood Pressure (BP) pre infusion and every 15 minutes during and after infusion.
- Monitor for signs of hypersensitivity and infusion reactions (hypertension, rash, headache) and anaphylaxis.
- Patients who have been treated with sarilumab may have a depressed C-Reactive Protein for some time following treatment.

Significant Adverse Drug Reactions

- Infection
- Hypersensitivity/infusion reactions (rash, headache, hypertension)
- Anaphylaxis
- Complications of diverticulitis

Safety Reporting

Any suspected adverse drug reactions (ADRs) for patients receiving sarilumab should be reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk/

Clinical Outcome Reporting

Hospitals managing COVID-19 patients are strongly encouraged to submit data through the ISARIC 4C Clinical Characterisation Protocol (CCP) case report forms (CRFs), as coordinated by the COVID-19 Clinical Information Network (CO-CIN) (https://isaric4c.net/protocols/)

References

- **UPDATED** Interim Clinical Commissioning Policy: Sarilumab for critically ill patients with COVID-19 pneumonia (adults). 17 February 2021 https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAttachment.aspx?Attachment_id=103774

- **UPDATED** COVID-19 Therapeutic Alert (CEM/CMO/2021/004). Interleukin-6 inhibitors (tocilizumab or sarilumab) for critically ill patients with COVID-19 pneumonia (adults). 17 February 2021 https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAttachment.aspx?Attachment_id=103780

- Summary of Product Characteristics. Sarilumab (Kevzara). Feb 2021. Found at www.medicines.org.uk

- Covid 19 rapid evidence summary – Sarilumab for COVID 19 https://www.nice.org.uk/advice/es34/chapter/Product-overview

- Medusa IV Drug Guide – Sarilumab https://medusa.wales.nhs.uk/IVGuideDisplayNewFormat.asp