Chief Medical Officer Directorate
Pharmacy and Medicines Division

Scottish Government
Riaghaltas na h-Alba
gov.scot

T: 0131-244-2528
E: irene.fazakerley@gov.scot

URGENT MESSAGE TO:

1. Directors of Pharmacy
2. Medical Directors NHS Boards

13 September 2021

Dear Healthcare Professional,

COVID THERAPEUTIC ALERT – INTERLEUKIN-6 INHIBITORS (TOCILIZUMAB OR SARILUMAB) FOR PATIENTS HOSPITALISED DUE TO COVID-19 .

Please see attached CMO letter about the combined policy replacing previous separately published policies for sarilumab and tocilizumab respectively on 17 February 2021. A single UK Interim Clinical Commissioning Policy has now been published, recommending that equal consideration is given to two potential interleukin-6 (IL-6) inhibitor treatment options - tocilizumab or sarilumab - for adult patients (aged 18 years and older) hospitalised due to COVID-19 in accordance with the agreed criteria for onward transmission as detailed below:-

Could all Directors of Pharmacy please forward this alert to:-

- Community Pharmacists
- Hospital Pharmacists
- Primary Care Pharmacists

Please could Medical Directors arrange to forward this alert on to:-

- General Practitioners
- Accident & Emergency Departments
- Nurses
- Consultants in Communicable Diseases
- Directors of Public Health
- Relevant Clinics
- Chief Executives of NHS Board

Thank you for your co-operation.

Yours sincerely

IRENE FAZAKERLEY
Medicines Policy Team

St Andrew's House, Regent Road, Edinburgh EH1 3DG
www.gov.scot

Department of Health & Social Care

NHS

COVID-19 Therapeutic Alert

This alert replaces the previous alert CEM/CMO/2021/006 issued on 17th February 2021

CEM/CMO/2021/016 12 September 2021

Interleukin-6 inhibitors (tocilizumab or sarilumab) for adult patients hospitalised due to COVID-19

Summary

A single UK Interim Clinical Commissioning Policy has now been published, recommending that equal consideration is given to two potential interleukin-6 (IL-6) inhibitor treatment options - tocilizumab or sarilumab - for adult patients (aged 18 years and older) hospitalised due to COVID-19 in accordance with the agreed criteria. The combined policy replaces previous separately published policies for sarilumab and tocilizumab respectively.

The policy takes into account evidence from the RECOVERY and REMAP-CAP trials, a rapid evidence review undertaken by the National Institute for Health and Care Excellence (NICE), updated guidelines (July 2021) from the World Health Organization (WHO) and currently available supplies of both medicines as a treatment for COVID-19 and other existing (routine) indications.

Action

NHS acute trusts / health boards are asked to take the following immediate steps to support treatment of adult patients hospitalised due to COVID-19:

1. **Organisations are recommended to consider prescribing either tocilizumab or sarilumab to adult patients hospitalised with COVID-19 in line with the criteria set out in the published policy.** In the absence of a confirmed virological diagnosis, tocilizumab or sarilumab should only be used when a multidisciplinary team has a high level of confidence that the clinical and radiological features suggest that COVID-19 is the most likely diagnosis.

2. Any organisation treating patients with either IL-6 inhibitor, as off-label products, will be required to assure itself that the necessary internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the health board / trust drugs and therapeutics committee, or equivalent.

3. In England, trusts who have not yet done so should register (by site) to participate in COVID-19 specific tocilizumab and sarilumab supply arrangements, respectively, via

Blueteq™. Blueteq should also then be used to confirm pre-authorisation for individual patients. Blueteq forms are now also available for post pubescent children under NHS England's Medicines for Children Policy. HSC Trusts in Northern Ireland should liaise with the Regional Pharmaceutical Procurement Service to register interest. In Scotland, Health Board Directors of Pharmacy should notify NHS National Procurement if they wish to participate. Health Boards in Wales should notify the All Wales Specialist Procurement Pharmacist of their intention to participate.

4. Order tocilizumab and sarilumab supply through existing (business as usual) routes. For those organisations who have formally confirmed they wish to participate, supply will be managed, where required, by providing an indicative maximum order 'cap' by hospital / trust. Retrospective reimbursement of medicines costs will continue to be managed as usual through the excluded drugs funding route in England. Further advice on this is available for Northern Ireland, Scotland and Wales.

5. Maintain access to intravenous tocilizumab for existing (non-COVID-19) indications including treatment of cytokine storm (CRS) following CAR-T cell therapy, rheumatoid arthritis (where appropriate), and paediatric indications.

6. Maintain access to subcutaneous sarilumab for existing rheumatoid arthritis patients.

7. Provide regular updates on the stock position to trust / hospital and regional pharmacy procurement lead / chief pharmacists.

Product Details

Tocilizumab (RoActemra®) is supplied to the UK by Roche CHUGAI. It is a humanised monoclonal antibody against the interleukin-6 (IL-6) receptor.

Tocilizumab for intravenous use has a marketing authorisation for adults in the treatment of moderate to severe rheumatoid arthritis. Tocilizumab for intravenous use has marketing authorisations for children 2 years and over in the treatment of active systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis and CAR-T induced cytokine release syndrome (CRS).

Sarilumab (Kevzara®) is supplied to the UK by Sanofi (Aventis Pharma Ltd). 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 published Interim Clinical Commissioning Policy cover off-label use of tocilizumab or sarilumab in adults as an intravenous infusion.

Prescribing

Tocilizumab and sarilumab are not licensed for use in COVID-19. As such, clinicians prescribing either tocilizumab or sarilumab for this indication should follow trust / hospital governance procedures in relation to the prescribing of off-label medicines.

Further guidance on the prescribing of off-label medicines can be found below:

- https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities
- https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines#paragraph-71

Administration

Tocilizumab should be administered as an intravenous infusion at a dose of 8mg per kg, up to a maximum dose of 800mg.

A single dose is to be administered. A second dose should not be considered, given the uncertainty over evidence of additional benefit as well as the need to maximise available supply.

Sarilumab should be administered as a single dose of 400mg (using 2 x 200mg pre-filled syringes) as an intravenous infusion.

The Medusa monograph is available here (registration / log-on required).

Neither tocilizumab nor sarilumab should be infused concomitantly in the same IV line with other medications.

Co-Administration

Corticosteroids
Administration of systemic dexamethasone or hydrocortisone is recommended in the management of patients with severe or critical COVID-19. Corticosteroids are not suggested in non-severe COVID-19 disease. Updated WHO guidance on the use of systemic corticosteroids in the management of COVID-19 can be found here. There is no interaction of tocilizumab or sarilumab with either dexamethasone or hydrocortisone expected.

Remdesivir
The Clinical Commissioning Policy for the use of remdesivir in hospitalised patients with COVID-19 who require supplemental oxygen can be found here. There is no interaction of either tocilizumab, or 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, tracking and follow-up

IL-6 inhibitors are immunosuppressants which can suppress C-Reactive Protein (CRP) response for up to 3 months after administration. Monitoring of longer-term progress is recommended via recruitment of patients receiving these agents to the ISARIC-CCP study. All handovers of clinical care (including between hospitals if patients are transferred, between levels of care and clinical teams within hospitals, and between hospitals and primary care) should explicitly mention that an IL-6 inhibitor has been given and the date of administration.

Distribution

NHS Trusts (NHS boards in Scotland and Wales)

Regional Medical Directors
Regional Chief Pharmacists
Lead/Senior Pharmacists and Regional Procurement Pharmacy Leads
Trust/Hospital Medical Directors to circulate to medical and nursing staff managing COVID-19 patients

Enquiries

England
Enquiries from NHS trusts in England should in the first instance be directed to your trust pharmacy team who will escalate issues to the Regional Chief Pharmacist and national teams if required. Further information can be requested from the dedicated email address: england.spoc-c19therapeutics@nhs.net.

Northern Ireland
Enquiries from hospitals in Northern Ireland should in the first instance be directed to your hospital pharmacy team who will escalate issues to the Regional Pharmaceutical Procurement Service or Pharmaceutical Directorate at the Department of Health if required Further information can be obtained by contacting RPHPS.Admin@northerntrust.hscni.net

Scotland
Enquiries from hospitals in Scotland should in the first instance be directed to your hospital pharmacy team who will escalate issues to either NHS National Procurement or the Scottish Government's Medicines Policy Team if required. Contact should be made using the following emails: nss.nhssmedicineshortages@nhs.scot or medicines.policy@gov.scot

Wales
Enquiries from hospitals in Wales should in the first instance be directed to the health board's Chief Pharmacist who will escalate issues to the Pharmacy and Prescribing Team at Welsh Government if required. Enquiries to the Welsh Government should be directed to: COVID-19.Pharmacy.Prescribing@gov.wales.

Rapid Policy Statement

Interim Clinical Commissioning Policy: IL-6 inhibitors (tocilizumab or sarilumab) for hospitalised patients with COVID-19 (adults)

12 September 2021

Commissioning position

The proposal is: IL-6 inhibitors tocilizumab and sarilumab are recommended to be available as treatment options through routine commissioning for adult patients (aged 18 years and older) hospitalised with COVID-19 in accordance with the criteria set out in this document.

Evidence and policy summary

In January 2021, the NHS published a UK Interim Position Statement on the use of IL-6 inhibitors in patients critically ill with COVID-19, based on emergent evidence from the REMAP-CAP trial demonstrating a clinical benefit with the use of tocilizumab or sarilumab in this population. In February 2021, the RECOVERY trial announced the findings of tocilizumab use in a broader hospitalised population, which indicated that tocilizumab significantly improved survival and other clinical outcomes in patients with hypoxaemia and systemic inflammation (severe COVID-19). The eligibility criteria for treatment with IL-6 inhibitors were then revised to reflect these findings, resulting in separate UK Clinical Commissioning Policies for each agent:

- Tocilizumab was recommended in the treatment of patients with severe or critical COViD-19
- Sarilumab was recommended in the treatment of patients with critical COVID-19

New evidence and guidance have since emerged to indicate the possibility of equivalence between the two IL-6 inhibitors. Further evidence from the REMAP-CAP trial has demonstrated equivalent effects of both IL-6 inhibitors on survival and requirement for organ support (84.9% posterior probability of equivalence) . A prospective meta-analysis of clinical trials of IL-6 inhibitors in patients hospitalized for COVID-19 showed that they were associated with lower 28-day all-cause mortality. These results led to a strong recommendation for the use of both IL-6 inhibitors (tocilizumab and sarilumab) to treat severe and critical COVID-19 in the World Health Organization (WHO) Therapeutics and

COVID-19 Living Guideline (WHO, 2021). The guideline, which was updated in July 2021, did not recommend the use of one IL-6 inhibitor over the other.

The NICE Rapid Guideline on managing COVID-19 (updated 2 September 2021) currently recommends the use of sarilumab for adults in hospital with COVID-19 if tocilizumab cannot be used or is unavailable. These guidelines were developed based on the consensus of a separate expert group and an independent evidence summary which states there is significant uncertainty around the efficacy and safety of sarilumab compared to standard care in treating patients with COVID-19. The rapid evidence summary does not consider the more recent evidence around the equivalence of IL-6 inhibitors and the meta-analysis which informed the WHO guidance.

This updated UK Clinical Commissioning Policy for IL-6 inhibitors considers the updated WHO guidance, the NICE rapid guideline and recent evidence around IL-6 inhibitors in the treatment of severe and critical COVID-19.

Implementation

Eligibility criteria

Patients must meet all the eligibility criteria and none of the exclusion criteria. Hospitalised patients are eligible[1] to be considered for **tocilizumab or sarilumab** if:

- COVID-19 infection is confirmed by microbiological testing or where a multidisciplinary team has a high level of confidence that the clinical and/or radiological features suggest that COVID-19 is the most likely diagnosis;

  AND

- They have not already been treated during this episode with tocilizumab or sarilumab;

  AND

- Receiving dexamethasone or an equivalent corticosteroid[2] (corticosteroid CAS alert) unless contraindicated;

  AND

  Either

  - Hypoxaemia with evidence of inflammation but not yet critically ill requiring respiratory support[3] defined as:

    - C-reactive protein level of at least 75mg/L; AND

[1] The decision to initiate treatment with tocilizumab or sarilumab should be made by the receiving consultant and with the support from multi-disciplinary colleagues in cases of uncertainty

[2] Patients are expected to be on a corticosteroid as the current standard of care, except where there is a strong contraindication against its use. Patients may be commenced on both a corticosteroid and tocilizumab simultaneously if deemed clinically appropriate.

[3] In the context of the COVID-19 pandemic, treatment of patients critically unwell with COVID-19 can be in the following (critical care equivalent) settings: designated intensive care unit (ICU); surge ICU; or other hospital settings delivering an equivalent level of respiratory care (such as respiratory ward, infectious disease ward).

- an oxygen saturation of <92% on room air OR requirement for supplemental oxygen;

Or

- In the early stages of critical illness requiring respiratory support (if an IL-6-inhibitor has not been already administered for COVID-19) defined as:
  - Within 48 hours[4] of commencement 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 cautions

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 of less than 150 x 10^9/L

Please refer to the Summary of Product Characteristics (SmPC) for tocilizumab and sarilumab for special warnings and precautions for use, although some may not be relevant for use in the acute setting, as the licensed indications address long-term use.

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

- Co-existing infection[5] that might be worsened by IL-6 inhibitor therapy
- A baseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than 5 times the upper limit of normal
- A pre-existing condition or treatment resulting in ongoing immunosuppression

Caution is also necessary when prescribing IL-6 inhibitors to patients with neutropaenia or thrombocytopaenia. Please note that C-reactive protein (CRP) levels may be depressed for some time after treatment with tocilizumab.

Pregnancy and women of childbearing potential

Tocilizumab and sarilumab should not be used during pregnancy unless clinically necessary.

The SmPC for tocilizumab currently states that: "*Women of childbearing potential must use effective contraception during and up to 3 months after treatment. There are no adequate data from the use of tocilizumab in pregnant women. A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose. The potential risk*

[4] Treatment should be started as early as possible

[5] 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.

for humans is unknown. RoActemra should not be used during pregnancy unless clearly necessary."

The SmPC for sarilumab currently states that: *"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. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Kevzara should not be used during pregnancy unless the clinical condition of the woman requires treatment with sarilumab."*

The SmPC for tocilizumab and sarilumab should be consulted if further information is required.

For women who are breast-feeding, the SmPCs for both tocilizumab and sarilumab state: *"It is unknown whether tocilizumab/sarilumab is excreted in human breast milk. The excretion of tocilizumab/sarilumab in milk has not been studied in animals. A decision on whether to discontinue breast-feeding or to discontinue IL-6 inhibitor therapy should be made taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman."*

Dose

Tocilizumab

The recommended dose of tocilizumab is 8mg/kg to be administered as an intravenous infusion. The total dose should not exceed 800mg. Tocilizumab should be diluted in a 100mL bag of 0.9% sodium chloride, after removing an equivalent volume of saline (total volume 100mL) and given over 1 hour[6].

A single dose is to be administered. A second dose should not be considered, given the uncertainty over evidence of additional benefit as well as the need to maximise available supply. Tocilizumab should not be infused concomitantly in the same IV line with other medications.

Sarilumab

The recommended dose of sarilumab is 400mg to be delivered as a once-only intravenous infusion. Sarilumab is available as a pre-filled syringe. For a 400mg dose two 200mg pre-filled syringes should be injected into a 100mL sodium chloride 0.9% infusion bag. The bag should be inverted at least 10 times to ensure thorough mixing and given over 1 hour[7].

Sarilumab should not be infused concomitantly in the same IV line with other medications**.** Further information on the use of sarilumab intravenously is available at: https://medusa.wales.nhs.uk/ (registration may be required).

[6] The following infusion rate is recommended: 10ml/hour for first 15 minutes then 130ml/hour for the remaining 45 minutes followed by a 20ml normal saline flush.
[7] The following infusion rate is recommended: 10ml/hour for first 15 minutes then 130ml/hour for the remaining 45 minutes followed by a 20ml normal saline flush

Co-administration

Corticosteroids

Administration of systemic dexamethasone or hydrocortisone is recommended in the management of patients with severe or critical COVID-19. Corticosteroids are not suggested in non-severe COVID-19 disease. Updated WHO guidance on the use of systemic corticosteroids in the management of COVID-19 can be found here. IL-6 inhibitors should not be regarded as an alternative to corticosteroids.

No interaction is expected between tocilizumab or sarilumab with either dexamethasone or hydrocortisone. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

Remdesivir

The Clinical Commissioning Policy for the use of remdesivir in hospitalised patients with COVID-19 who require supplemental oxygen can be found here. No interaction is expected between tocilizumab or sarilumab with remdesivir. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

Safety reporting

These medicines do not yet have a licence (marketing authorisation) for use in COVID-19 and therefore it is vital that any serious suspected adverse reactions are reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk/.

In addition, treatment with IL-6 inhibitors can lower the ability of the immune system to fight infections. This could increase the risk of getting a new infection or make any infection the patient contracts worse. It also causes prolonged depression of CRP levels, making CRP a less reliable marker of active infection. All handovers of clinical care (including between hospitals if patients are transferred, between levels of care and clinical teams within hospitals, and between hospitals and primary care) must explicitly mention that an IL-6 inhibitor has been given and the date of administration. Clinicians must ensure the GP is aware the patient has received an IL-6 inhibitor and provide information to the patient to such effect.

Marketing authorisation

Tocilizumab

Tocilizumab delivered intravenously has marketing authorisation for use in moderate to severe active rheumatoid arthritis, some forms of juvenile idiopathic arthritis and for cytokine release syndrome as part of CAR-T therapy. NHS England also commissions off-label use of tocilizumab for Takayasu arteritis and Still's Disease. **The use of tocilizumab in COVID-19 is off-label.**

Sarilumab

Sarilumab has marketing authorisation for subcutaneous use in adults with moderate to severe active rheumatoid arthritis. **The use of sarilumab intravenously in COVID-19 is off label.**

Governance

Off-label use of medication

Any provider organisation treating patients with these interventions will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the health board/hospital/trust's drugs and therapeutics committee, or equivalent.

Data collection requirement

Provider organisations in England should register all patients using prior approval software (alternative arrangements in Scotland, Wales and Northern Ireland will be communicated) and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

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/).

Effective from

This policy will be in effect from the date of publication.

Policy review date

This is an interim rapid clinical policy statement, which means that the full process of policy production has been abridged: public consultation has not been undertaken. This policy may need amendment and updating if, for instance, new trial data emerges, supply of the drug changes, or a new evidence review is required. A NICE Technology Appraisal or Scottish Medicines Consortium (SMC) Health Technology Assessment or All Wales Medicines Strategy Group (AWMSG) appraisal of tocilizumab for COVID-19 would supersede this policy when completed.

Equality statement

Promoting equality and addressing health inequalities are at the heart of the four nations' values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010 or equivalent equality legislation) and those who do not share it; and

- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

COVID-19	Refers to the disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus
High-flow nasal cannula	An oxygen supply system capable of delivering up to 100% humidified and heated oxygen at a flow rate of up to 60L/minute
Continuous positive airway pressure	A type of positive airway pressure in which air flow is introduced into the airways to maintain a continuous pressure that constantly keeps the airways open
Non-invasive ventilation	The administration of breathing support for those unable to breathe on their own without using an invasive artificial airway
Invasive mechanical ventilation	A life support treatment which helps people breathe using an invasive artificial airway when they are not able to breathe enough on their own

References

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5. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Shankar-Hari M, Vale CL, et al. Association Between Administration of IL-6 Antagonists

and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. *JAMA*. 2021;326(6):499-518. doi:10.1001/jama.2021.11330