Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

HSE Interim Guidance for the use of Tocilizumab in the Management of Hospitalised Patients with Severe COVID-19 Disease

This document is intended for use by healthcare professionals only.

This guidance is specific to the management of hospitalised patients with severe COVID-19 disease.

While the guidance is intended to strengthen clinical management of these patients it does not replace clinical judgment or specialist consultation.

This guidance should be read in conjunction with the National HSE Infection Prevention and Control (IPC) Guidance for Possible or Confirmed COVID-19 .

Guideline: HSE Interim Guidance for the use of Tocilizumab in the Management of Hospitalised Patients with Severe COVID-19 Disease		Published: 15 Jan 2021 Review: 31 Mar 2021	Version number:6
Protocol Code: COVID19-TOCILIZUMAB	Approved by: Dr Vida Hamilton, HSE National Clinical Advisor and Group Lead, Acute Hospitals	Contributors: Prof C Bergin, Prof P Browne, Dr C Oloughlin, Dr D Murphy, Dr L Bacon, Prof J Laffey, Prof A Nichol, Prof D Kane, Dr R Adams, F King, P Gilvarry.	Page 1 of 5

This guidance document is informed by the evidence reported in the COVID-19 ERG Rapid Evidence Review "Tocilizumab in the Management of COVID-19 Version 5" published on 23 October 2020 (available from: https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/rapid-evidence-reviews.html), the preliminary report (pre-print) from the REMAP-CAP[1] study and the published EMPACTA[2] study.

The following HSE interim guidance and advisory statements should also be considered for the management of patients with COVID-19, as appropriate:

- *COVID-19 Interim Clinical Guidance - VTE protocol and patient information for acute hospitals (available from: https://hse.drsteevenslibrary.ie/c.php?q=679077&p=4866382)*
- *The following interim guidance and advisory statements available from https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/:*
    - *HSE Interim Guidance for the Use of Antiviral Therapy in the Clinical Management of Acute Respiratory Infection with SARS-CoV-2 (COVID-19)*
    - *HSE Interim Position Statement on the Use of Human Normal Intravenous Immunoglobulin (IVIg) in the Management of COVID-19.*
    - *HSE Interim Guidance for the use of Systemic Corticosteroids in the Management of Hospitalised Patients with Severe COVID-19 Disease*

Section 1: Summary Guidance for the use of Tocilizumab in the Management of Patients with Severe COVID-19.

1. A preliminary report from the REMAP-CAP trial suggests possible benefits with the use of IL6-inhibitors (tocilizumab or sarilumab) in critically ill COVID-19 patients admitted to intensive care (ICU).[1] The data are available as a pre-print only and are not yet peer-reviewed. Most patients evaluated in the REMAP-CAP trial were also treated with a corticosteroid and the reported benefits are thought to be supplementary to those from corticosteroids.

2. Published data from the EMPACTA study suggests possible benefit with the use of tocilizumab in non-ICU hospitalised patients with COVID-19 pneumonia who were not receiving mechanical ventilation.[2] More than 25% of the patients in EMPACTA were older than 65 years of age, more than 75% had at least one coexisting condition, and more than 80% were in a minority racial or ethnic group.

[1] The REMAP-CAP Investigators. Interleukin-6 Receptor Antagonists in Critically Ill Patients with COVID-19 – Preliminary Report. medRxiv 2021.01.07; doi: https://doi.org/10.1101/2021.01.07.21249390.

[2] Salama C, Han J, Yau L, et al. Tocilizumab in Patients Hospitalised with COVID-19 Pneumonia. N Engl J Med

3. The HSE recommends that the use of tocilizumab in a defined cohort of patients infected with COVID-19 should be considered after consultant-level discussion in a multidisciplinary setting that includes colleagues from critical care medicine, haematology, infection specialists, respiratory medicine, and with patient engagement (or their relevant person, by phone). See **Section 2** for patient selection criteria.

4. The potential for adverse events resulting from intravenous tocilizumab therapy must be considered before initiating therapy in patients with COVID-19. Notably, no new safety signals associated with intravenous tocilizumab were reported from the EMPACTA study or the preliminary report from the REMAP-CAP study.

5. Patients should continue to be enrolled in clinical trials, including trials to assess the safety and efficacy of IL6 -inhibitors compared to other immunomodulatory agents, wherever possible. Information on on-going clinical trials, including those recruiting, is available on the EU CT Register for COVID trials (https://www.clinicaltrialsregister.eu/ctrsearch/search?query=covid-19) or www.clinicaltrials.gov .

6. There is a limited global supply of intravenous tocilizumab and judicious consideration before use is advised. Use should be restricted to clinical scenarios with potential for treatment benefit.

7. The use of tocilizumab in the management of COVID-19 is off-label. Off-label use of medicines should be managed under existing local hospital governance arrangements. The State Claims Agency advise that if a clinician should prescribe and/or administer an off-label medication with the explicit knowledge and authority of the hospital, the Clinical Indemnity Scheme will indemnify the hospital/clinician.

8. This guidance document replaces the *HSE Interim Advisory Statement for the use of Tocilizumab in the Management COVID-19*. The use of tocilizumab and other IL-6 modulating therapies continue to be investigated for the management of COVID-19 in a number of on-going clinical trials, including the RECOVERY and REMAP-CAP trials. Full publication of these and other studies will help inform future HSE recommendations.

Section 2: Patient Selection

1. Intravenous tocilizumab should only be considered for the management of COVID-19 disease in hospitalised patients with an inadequate clinical response to *systemic corticosteroid therapy requiring:

    a. ICU admission with severe pneumonia and requiring organ support

    OR

    b. Non-ICU patients with COVID Respiratory Scale (CRS) category C1 or C2 disease.

    The HSE National Clinical Programme for Respiratory Medicine/Irish Thoracic Society CRS is available from *https://hse.drsteevenslibrary.ie/c.php?g=679077&p=4866795#appendix1%20021*

    AND

2. Exclusion of contraindications to intravenous tocilizumab, including acute severe infection from sources other than SARS-CoV2^.

    AND

3. If treatment is being considered, it should only be initiated after consultant-level discussion in a multidisciplinary setting that includes critical care medicine, haematology, infection specialists, respiratory medicine, and with patient engagement (or their relevant person, by phone).

*_HSE Interim Guidance for the use of Systemic Corticosteroids in the Management of Hospitalised Patients with Severe COVID-19 Disease_ is available from: https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/hse-interim-guidance-for-the-use-of-systemic-corticosteroids-in-the-management-of-hospitalised-patients-with-severe-covid-19-disease.pdf .

^Suspected co-infection with pathogens other than SARS-CoV2 should be investigated and treated empirically as per local antimicrobial policy with consideration of the principles of antimicrobial stewardship (Further information available from: https://www.hpsc.ie/az/respiratory/coronavirus/novelcoronavirus/guidance/infectionpreventionandcontrolguidance/antimicrob ialstewardship/

Section 3 Key Prescribing Information

Key Prescribing Information *Adapted from Summary of Product Characteristics[3] for tocilizumab (RoActemra®) and the REMAP-CAP study protocol[4].* *Refer to the Summary of Product Characteristics[3] for tocilizumab for full prescribing information.*	
Recommended Dose Schedule in Adults (Specialist Paediatric advice required for patients aged under 18 years old)	- Tocilizumab should be administered as a single intravenous infusion at a dose of 8mg/kg (maximum 800mg per dose). - Dose rounding to the nearest whole vial is recommended. Vial sizes available may include 80mg, 200mg, and 400mg. - In exceptional circumstances, one additional dose may be considered 12-24 hours after the initial dose if there has not been sufficient clinical improvement. - The decision to administer a second dose must only be made following consultant-level multidisciplinary specialist input (see **Section 2**). - A maximum of two doses per course is recommended; subject to drug access.
Method of Administration for Adult Patients >30kg (Specialist Paediatric advice required for patients aged under 18 years old)	- Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 100 mL infusion bag, equal to the volume of RoActemra® concentrate required for the patients dose, under aseptic conditions.[3] - The required amount of RoActemra® concentrate (0.4 mL/kg) should be withdrawn from the vial and placed in the 100 mL infusion bag. This should be a final volume of 100 mL. To mix the solution, gently invert the infusion bag to avoid foaming.[3] - After dilution, RoActemra® should be administered as an intravenous infusion over 1 hour.[3]

[3] Summary of Product Charateristics. RoActemra 20 mg/mL concentrate for solution for infusion. Available online from: https://www.medicines.ie/medicines/roactemra-20-mg-ml-concentrate-for-solution-for-infusion--33648/spc .

[4] REMAP-CAP Study Protocol. *Domain-Specific Appendix: COVID-19 Immune Modulation Therapy.* Available online from: https://www.remapcap.org/protocol-documents .