Application for Inclusion of Tocilizumab (an Interleukin-6 [IL-6] receptor blocker) to the World Health Organization's Model Lists of Essential Medicines and Essential Medicines for Children

1 Summary statement of the proposal for inclusion

Cumulative cases of Covid-19 are over 642 million, with 6.6 million global deaths.[1] Vaccination is having a substantial impact on hospitalizations and death in a number of high-income countries, but limitations in global access to COVID-19 vaccines mean that many populations remain vulnerable. There remains a need for more effective treatments for COVID-19.

WHO guidance makes a strong recommendation for the use of Interleukin-6 (IL-6) receptor blockers for patients with severe and critical Covid-19, including tocilizumab and sarilumab. The benefit is a reduction in mortality of 16 per 1000 people treated, which combines evidence for both compounds, and is judged to be high certainty evidence. A separate meta-analysis concluded that tocilizumab probably results in slightly fewer serious adverse events than standard care alone or placebo (RR 0.89, 95% CI 0.75 to 1.06, moderate certainty evidence).

It is likely that there is a therapeutic class effect for these medications, as is demonstrated in the use for rheumatological indications. Tocilizumab and sarilumab are the best studies, with significant evidence from randomised controlled trials in Covid-19. Others within this class include clazakizumab, olokizumab, situximab, and levilimab. **Within this application, we propose a square box indication for tocilizumab**, which relates to both the Model List of Essential Medicines and the Essential Medicines for Children.

The evidence for benefit derives from prospective meta-analysis which is the basis of all of the WHO Therapeutics and COVID-19 Living Guidelines; these are summarised here. These guidelines support global use of the medicine.[2] This application will ensure that the Essential Medicines List reflects current evidence-based guidance, and supports international work through the ACT-Accelerator to make effective therapies available in an equitable and transparent manner.[3]

2 Relevant WHO technical department and focal point

Janet Diaz, Clinical Management Unit, Country Readiness Strengthening, HQ.

3 Name of organisation(s) consulted and/or supporting the application

The WHO Guideline Development Group for Covid-19 therapeutics has developed and published recommendations on the use of this medicine.[2]

4 International names for medicine within this application

4.1 International non-proprietary name (INN)

tocilizumab

4.2 Anatomical Therapeutic Chemical code (ATC)

L04AC07

5 Dose

When given for COVID-19, tocilizumab is administered as single intravenous doses, typically over 1 hour. Tocilizumab is dosed at 8mg/kg, up to a maximum of 800 mg.[4]

No dose adjustment is required in patients with mild renal impairment. Tocilizumab has not been studied in patients with moderate to severe renal impairment, nor in hepatic impairment.[4]

Note: A second dose may be administered 12 to 48 hours after the first dose; this was offered variably in major clinical trials at the discretion of treating clinicians if a clinical response was felt to be inadequate. Concurrent systemic corticosteroids should be given, typically for up to 10 days, though this may vary between 5 and 14 days.

6 Whether listing is requested as an individual medicine or as representative of a pharmacological class

This application is for listing tocilizumab as a representative of a pharmacological class (IL-6 receptor blockers), which also includes sarilumab.

7 Treatment details

7.1 Requirements for diagnosis

The medication should ideally be administered within five days of symptom onset. Diagnostic possibilities include rapid diagnostic tests (RDT) and polymerase chain reaction

(PCR), both of which are supplied by multiple manufacturers. There is no stated preference for diagnostic approach within the guidance, although it is noted that:

> *…availability and use of appropriate SARS-CoV-2 diagnostic tests is needed to improve access to drugs, especially those targeting the early phase of disease. The appropriate use of rapid diagnostic tests such as antigen-detection assays can improve early diagnosis in the community and in primary health care settings. Health care systems must, however, gain expertise in choosing and implementing rapid tests, choosing those most applicable to their settings.*

7.2 Requirements for treatment and monitoring

IL-6 receptor blockers should be initiated with systemic corticosteroids; specific timing during hospitalization or the course of illness is not specified. There is no stipulated monitoring regimen.

Routine bloodwork including neutrophil count, platelets, transaminases, and total bilirubin should be checked prior to initiation of therapy. All patients should be monitored for signs and symptoms of infection, as the general effect of immunomodulation may either unmask or reactivate sub-clinical infection (for example, tuberculosis), or make recipients more prone to the consequences of new infection. The specific monitoring will be determined by the treating physician, taking into consideration the prevalence of different infections within their region.

8 Mechanism of action

IL-6 is a pleiotropic cytokine which activates and regulates the immune response to infections. Elevated IL-6 concentrations are associated with severe outcomes in COVID-19, including respiratory failure and death, although the role of IL-6 in disease pathogenesis is unclear.

Tocilizumab and sarilumab are monoclonal antibodies initially approved for use in rheumatoid arthritis. They antagonize the membrane bound and soluble forms of the IL-6 receptor (IL-6R/sIL-6R). Tocilizumab is approved for intravenous use in rheumatoid arthritis and sarilumab for subcutaneous use, although in COVID-19 both have been studied intravenously. At the studied doses in COVID-19, both medicines are expected to achieve very high levels of receptor occupancy based upon studies in rheumatoid arthritis. IL-6

receptor blockers are being repurposed in terms of indication but not in terms of the primary pharmacological mechanism of action. Efficacy in COVID-19 depends upon the importance of IL-6 signalling in the pathophysiology of the disease, rather than upon whether the doses used achieve target concentrations.

9 Review of benefits (summary of evidence of comparative effectiveness)

A strong recommendation for IL-6 receptor blockers for patients with severe COVID-19 were published on 06 July 2021 as the sixth version of the WHO living guideline. They were augmented in the twelfth version as evidence became available supporting the concomitant use of not only corticosteroids (as originally recommended), but also baricitinib.

The strong recommendation for use was made on the basis of systematic review showing high certainty evidence of improved survival and reduction in need for mechanical ventilation. For mortality, the odds ratio comparing IL-6 receptor blockers with standard care was 0.86 (95%CI 0.79-0.95) based on 10930 participants in 27 studies. This represented 16 fewer deaths per 1000 in the IL-6 blocker group.

Figure 1 – Graphical evidence summary of the benefit of tocilizumab for severe and critical Covid-19 disease[2]

The interpretations forming the recommendation[2] are given below:

> *IL-6 receptor blockers reduce mortality and need for mechanical ventilation based on high certainty evidence. Low certainty evidence suggests they may also reduce duration of mechanical ventilation and hospitalization.*[5,6] *The RECOVERY trial demonstrating reduced risk of death also in patients already receiving corticosteroids and IL-6 receptor blockers., resulting in an updated recommendation to allow the combination of IL-6 receptor blockers and baricitinib in the twelfth iteration of this WHO guideline.*
>
> *Subgroup analyses indicated no effect modification based on IL-6 receptor blocker drug (sarilumab or tocilizumab) or disease severity (critical vs severe) and therefore this recommendation applies to all*

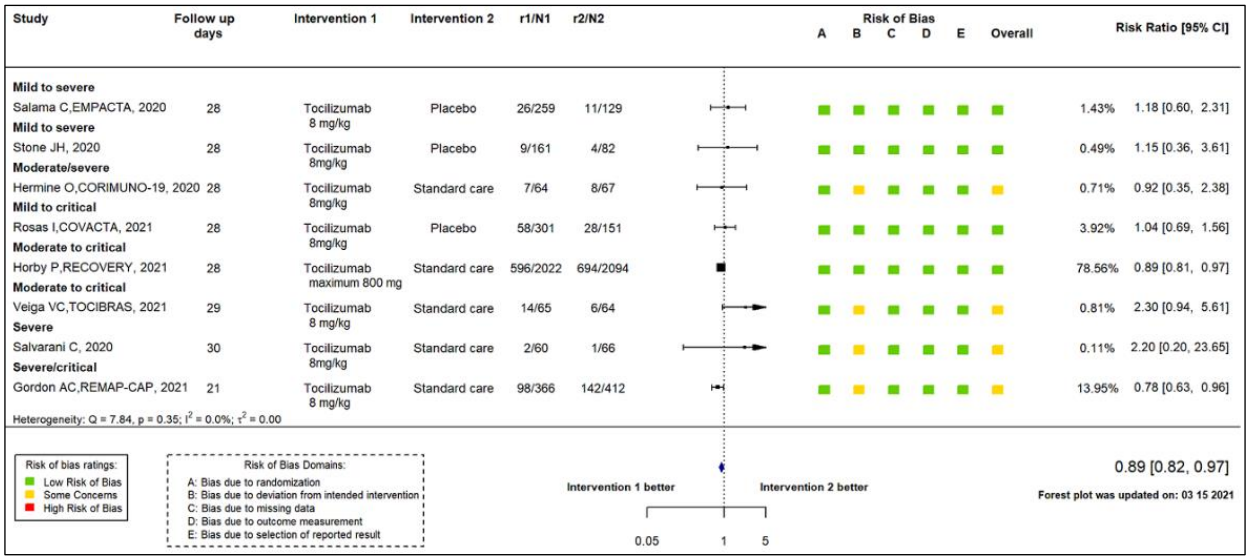
> *adult patients with either severe or critical COVID-19.[7] … Subgroup analyses evaluating baseline steroid use found greater benefit of IL-6 receptor blockers in patients receiving steroids compared with those who were not (p=0.026), demonstrating that steroid use does not abolish and might enhance the beneficial effect of IL-6 receptor blockers.*

The certainty of evidence within the WHO Living Guidelines systematic review was summarised as follows:[2]

> *Certainty of evidence was rated as high for mortality and need for mechanical ventilation. Certainty in duration of mechanical ventilation was rated as low due to serious risk of bias due to concerns regarding lack of blinding in included trials, and for imprecision as the lower limit of the confidence interval suggested no effect. Certainty in duration of hospitalization was rated as low due to serious risk of bias from lack of blinding in included trials, and for inconsistency related to differences in point estimates and lack of overlap in confidence intervals.*
>
> *Certainty in serious adverse events was rated as very low due to risk of bias related to lack of blinding and ascertainment bias, and very serious imprecision due to very wide confidence intervals which did not rule out important benefit or harm; certainty in risk of bacterial or fungal infections was rated as low due to similar concerns regarding serious risk of bias and serious imprecision.*

A Cochrane review found similarly: that tocilizumab reduces all-cause mortality at D28 compared to standard care alone or placebo (RR 0.89, 95% CI 0.82 to 0.97; I^2 = 0.0%; 8 RCTs, 6363 participants; absolute effect: 32 fewer deaths per 1000 (from 52 fewer to 9 fewer); high-certainty evidence), see Figure 2.[8] Within this meta-analysis, 9 studies contributed data on tocilizumab,[9-16] and 2 on sarilumab.

Figure 2 – Graphical evidence summary of the effect of tocilizumab on all-cause mortality at 28 days for Covid-19 disease[8]



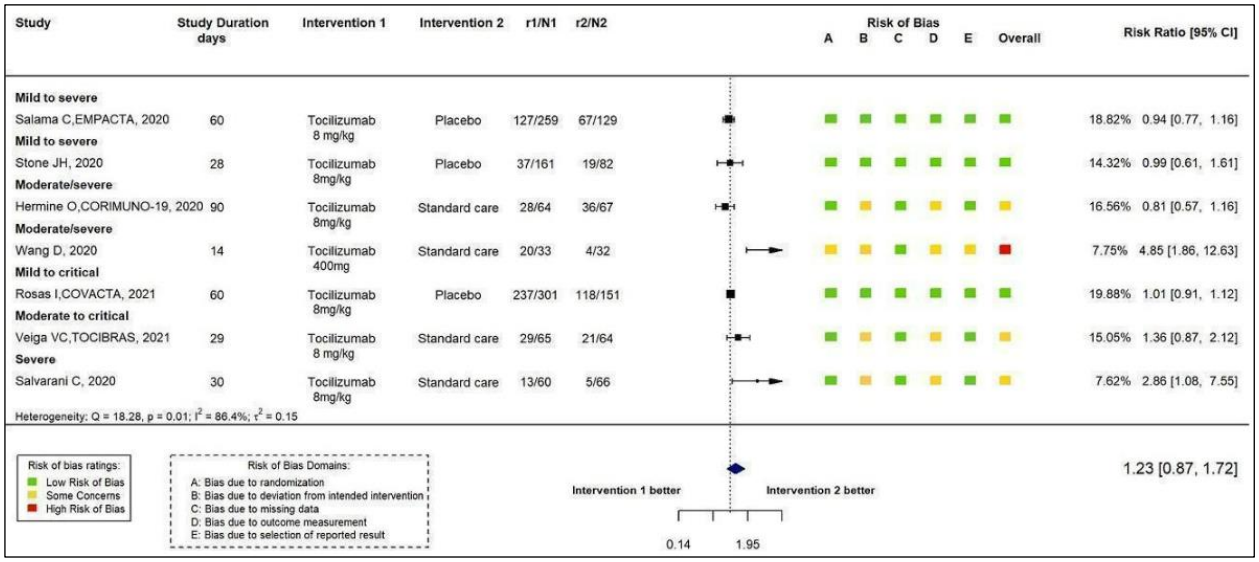
10 Review of harms and toxicity (summary of evidence of safety)

The WHO living guidelines (v12) considered available evidence on SAEs.[2] It was noted that:

> *The GDG acknowledged the uncertain data regarding SAEs and bacterial infections, but felt that the evidence of benefit for the two most important patient outcomes warranted a strong recommendation.*

A Cochrane review of safety noted high uncertainty about the effect of tocilizumab on adverse events (RR 1.23, 95% CI 0.87 to 1.72; I^2 = 86.4%; 7 RCTs, 1534 participants; very low-certainty evidence).[8] This review concluded that tocilizumab probably results in slightly fewer serious adverse events than standard care alone or placebo (RR 0.89, 95% CI 0.75 to 1.06; I^2 = 0.0%; 8 RCTs, 2312 participants; moderate-certainty evidence), see Figure 3.

Figure 3 – Graphical evidence summary of the adverse effects of tocilizumab when used for Covid-19 disease[8]



Adverse events listed within the SmPC are:

- Very common (≥ 1/10): upper respiratory tract infections, hypercholesterolaemia
- Common (≥1/100 to <1/10): cellulitis, pneumonia, oral herpes simplex, herpes zoster, leucopenia, hypofibrinogenaemia, headache, dizziness, conjunctivitis, hypertension, cough, dyspnoea, abdominal pain, mouth ulceration, gastritis, rash, pruritis, urticaria, peripheral oedema, hypersensitivity reactions, raised hepatic transaminases, weight increases.
- Uncommon (≥1/1,000 to <1/100): diverticulitis, hypothyroidism, hypertriglyceridaemia, stomatitis, gastric ulcer, nephrolithiasis
- Rare (≥ 1/10,000 to < 1/1,000): anaphylaxis, drug induced hepatic injury, Stevens-Johnson syndrome

10.1 Contraindications

The US FDA note that tocilizumab and sarilumab should be used with caution in patients with COVID-19 who belong to populations that have not been adequately represented in clinical trials.[17] This includes patients who are significantly immunosuppressed, particularly those who have recently received other biologic immunomodulating drugs, and patients with any of the following:

- Alanine transaminase levels >5 times the upper limit of normal
- A high risk for gastrointestinal perforation
- An uncontrolled serious bacterial, fungal, or non-SARS-CoV-2 viral infection
- Absolute neutrophil counts <500 cells/µL
- Platelet counts <50,000 cells/µL
- Known hypersensitivity to tocilizumab or sarilumab

10.2 Use in specific populations

There are insufficient data to determine whether there is a tocilizumab-associated risk for major birth defects or miscarriage. As pregnancy progresses, monoclonal antibodies are actively transported across the placenta (with the greatest transfer occurring during the third trimester), and this may affect immune responses in the exposed fetus. Given the paucity of data, current recommendations for rheumatological indications advise against the use of tocilizumab during pregnancy.[18] The NIH note however that:

> *Whether to use tocilizumab during pregnancy should be a joint decision between the pregnant individual and their health care provider, and the decision-making process should include a discussion of the potential risks and benefits.*[17]

The WHO GDG reflected this, saying "*it is uncertain what effect transient immunosuppression in the fetus may have and this should be weighed against the potential benefit for the mother*."[2]

For children, the WHO Therapeutics and COVID-19 guideline states:[2]

> *None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. However, the GDG had no reason to think that children with COVID-19 would respond any differently to treatment with IL-6 receptor blockers. This is especially true given tocilizumab is used in children safely for other indications including polyarticular juvenile rheumatoid arthritis, systemic onset of juvenile chronic arthritis, and chimeric antigen receptor T-cell induced cytokine release syndrome. Sarilumab is not approved in children, so if an IL-6 receptor blocker is used in this population, tocilizumab is*

> *preferred. The GDG also recognized that in many settings children are commonly admitted to hospital with acute respiratory illnesses caused by other pathogens; as a result, it may be challenging to determine who is ill with severe COVID-19, even with a positive test, and therefore likely to benefit from IL-6 receptor blockade.*

11 Summary of available data on comparative cost and cost-effectiveness of the medicine

There is currently no formal cost-effectiveness analysis as part of the WHO guideline. Please see below for changes in market availability.

12 Summary of regulatory status and market availability

Currently, tocilizumab is pre-qualified for Covid-19, and is provided commercially by the patent holder, Roche, which has committed up to 250,000 doses through the ACT-Accelerator partnership platform.[19] Sarilumab is under patent by Sanofi Genzyme. Neither is part of the Medicines Patent Pool initiative.

Modelling results have estimated US dollar costs per quality-adjusted life-year, finding the incremental cost-effectiveness ratio for combination therapy of tocilizumab compared with dexamethasone alone to be $16 520 (95% credible interval, $10 760–$51 350) and $26 840 (95% credible interval, $14 800–$101 030) in the higher and lower mortality scenarios respectively.[20] Willingness-to-pay thresholds are lower in low- and middle-income countries compared with the United States.

13 Availability of pharmacopoeia standards

Tocilizumab is listed in the British National Formulary with a specific indication for Covid-19.[21] Sarilumab is listed for rheumatological indications, but not specifically for Covid-19.

References

1. World Health Organisation. WHO Coronavirus (COVID-19) Dashboard. World Health Organization; 2022.

2. World Health Organisation. Therapeutics and COVID-19: living guideline (12th edition), 2022.

3. World Health Organisation. The Access to COVID-19 Tools Accelerator. 2022. https://www.act-a.org/ (accessed 08/12/2022.

4. Roche Products Limited. SmPC for RoActemra 20mg/ml Concentrate for Solution for Infusion [tocilizumab]. 2022.

5. Zeraatkar D, Cusano E, Martínez JPD, et al. Use of tocilizumab and sarilumab alone or in combination with corticosteroids for covid-19: systematic review and network meta-analysis. *BMJ Medicine* 2022; **1**(1): e000036.

6. The WHOREAfC-TWG. Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. *Jama* 2021; **326**(6): 499-518.

7. Schandelmaier S, Briel M, Varadhan R, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 2020; **192**(32): E901-e6.

8. Ghosn L, Chaimani A, Evrenoglou T, et al. Interleukin-6 blocking agents for treating COVID-19: a living systematic review. *Cochrane Database of Systematic Reviews* 2021; (3).

9. Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med* 2021; **181**(1): 32-40.

10. Rosas IO, Bräu N, Waters M, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. *New England Journal of Medicine* 2021; **384**(16): 1503-16.

11. Salama C, Han J, Yau L, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. *New England Journal of Medicine* 2020; **384**(1): 20-30.

12. Salvarani C, Dolci G, Massari M, et al. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med* 2021; **181**(1): 24-31.

13. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. *The New England journal of medicine* 2020; **383**(24): 2333-44.

14. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. *New England Journal of Medicine* 2021; **384**(16): 1491-502.

15. Horby PW, Pessoa-Amorim G, Peto L, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. *Medrxiv* 2021.

16. Veiga VC, Prats J, Farias DLC, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. *BMJ (Clinical research ed)* 2021; **372**: n84.

17. National Institutes for Health. NIH Covid-19 treatment guidelines: Interleukin-6 Inhibitors. 2022.

18. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. *Arthritis Rheumatol* 2020; **72**(4): 529-56.

19. World Health Organisation. Joint Statement from Unitaid and the World Health Organization (on behalf of the Access to COVID-19 Tools Accelerator) regarding availability of tocilizumab. 2021.

20. Sinha P, Linas BP. Combination Therapy With Tocilizumab and Dexamethasone Cost-Effectively Reduces Coronavirus Disease 2019 Mortality. *Clinical Infectious Diseases* 2021; **73**(11): 2116-8.

21. Joint Formulary Committee. British National Formulary (BNF). 2022.