## Introduction[1,2,3]

Tocilizumab is provisionally registered by the Therapeutic Goods Administration for use in Australia for treatment of adults with COVID-19. The National COVID-19 Clinical Evidence Taskforce also provides a conditional recommendation to consider using tocilizumab for pregnant or breastfeeding women and children or adolescents who require supplemental oxygen, particularly where there is evidence of systemic inflammation.

Tocilizumab is not an alternative or substitute for vaccination. **Vaccination is the preferred and primary option for the prevention of COVID-19.**

This guideline requires endorsement by your local Drug and Therapeutics Committee prior to implementation. Additional resources to support the safe and appropriate use of tocilizumab are available here.

## Drug class and mechanism of action[3,4]

In severe disease states, an overactive immune response can result in increased production of cytokines, such as interleukin-6, exacerbating inflammation and delaying recovery. Tocilizumab is a recombinant humanised monoclonal antibody which binds to the receptors of the cytokine interleukin-6, reducing inflammation and improving ability to recover from COVID-19 infection.

## Approved indication[3,5,6]

Treatment of COVID-19 in hospitalised adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. The National COVID-19 Clinical Evidence Taskforce also provides a conditional recommendation for use in the following patient groups:

- Pregnant and breastfeeding women – dosing based on body weight at time of clinical need, see conditional recommendation for further details.
- Children and adolescents – see conditional recommendation for further details.

## Contraindications and precautions[4,7,9]

- Patients with a history of any reaction consistent with hypersensitivity to any component of the product, Chinese hamster ovary cell products or other recombinant human or humanised antibodies. Use with caution in patients with a history of anaphylaxis to other medicines.
- Safety and efficacy of tocilizumab in children and adolescents aged 18 years and younger with conditions other than paediatric juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis and cytokine release syndrome has not yet been established. See National COVID-19 Clinical Evidence Taskforce guidance for further informationregarding use in COVID-19.
- Patients with sepsis or active, severe infections from non-COVID-19 pathogens.
- Use with caution if patient has a history of recurring or chronic infection, or underlying conditions (e.g. diabetes) which may predispose them to infections. Patients using tocilizumab may be susceptible to opportunistic infections, reactivation of latent tuberculosis and viruses such as hepatitis.
- Avoid concurrent immunosuppressive/anti-rejection therapy to reduce risk of infection.
- Use with caution if patient has current or previous diverticulitis or intestinal ulceration. Patients presenting with symptoms potentially indicating gastrointestinal perforation should be evaluated promptly.

- **Tocilizumab use may result in hepatotoxicity**. In COVID-19 patients, tocilizumab is not recommended if transaminases ALT or AST > 10 times upper limit of normal (ULN).
- In COVID-19 patients, tocilizumab is not recommended if platelets < 50 x $10^9$/L and absolute neutrophil count (ANC) < 1 x $10^9$/L.
- See *Pregnancy and breastfeeding* section for recommendations in pregnancy and breastfeeding.

## Pregnancy and breastfeeding[4,5]

Pregnancy

Tocilizumab has been classified **pregnancy category C** by the Therapeutic Goods Administration and there is no established data for use in these patients with COVID-19. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by treating health professionals. See National COVID-19 Clinical Evidence Taskforce guidance for further information.

For the babies of women who received tocilizumab during pregnancy (after 20 weeks of gestation), live vaccines (rotavirus and BCG) should be avoided in the first six months of life. All non-live vaccinations are safe and should be undertaken (see National COVID-19 Clinical Evidence Taskforce factsheet).

Breastfeeding

It is unknown whether tocilizumab is excreted in human breast milk and its efficacy and safety in lactating women has not been established. A decision whether to discontinue breastfeeding or to abstain from tocilizumab therapy should consider the benefit of breastfeeding for the baby and the benefit of therapy for the woman. See National COVID-19 Clinical Evidence Taskforce guidance for further information.

## Drug interactions[5,8,9]

Potential drug interactions have not been investigated in patients with COVID-19. Resources such as the Liverpool COVID-19 drug interactions tool and Micromedex drug interactions tool may be useful to check for specific drug-drug interactions. Generally:

- Concurrent use of tocilizumab with immunosuppressive/anti-rejection therapy may increase risk of infection.
- The cytokine interleukin-6 suppresses expression of the drug metabolising enzymes (cytochromes) CYP450, CYP3A4 and to a lesser extent, CYP1A2, CYP2C9 and CYP2C19. Tocilizumab inhibits interleukin-6, potentially reversing its suppressing impact on cytochrome expression. Tocilizumab itself does not inhibit or induce cytochromes.
- Drugs metabolised via the above cytochromes (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporin or benzodiazepines) should be monitored as doses may need to be adjusted to maintain therapeutic effect, particularly CYP450 substrates with a narrow therapeutic index.
- Note that indirect effects of tocilizumab on cytochrome activity may persist for several weeks after stopping therapy.
- Live and live-attenuated vaccines should not be given concurrently as clinical safety has not been established. Contact the NSW Immunisation Specialist Service (NSWISS) Advice Line (1800 679 477) for further advice.

## Presentation, storage and stability[4,10]

Tocilizumab is available as:

- 80 mg/4 mL concentrate solution for intravenous infusion vial
- 200 mg/10 mL concentrate solution for intravenous infusion vial
- 400 mg/20 mL concentrate solution for intravenous infusion vial

For images of available products, refer to CEC factsheet.

- Store vials at 2–8°C and keep the container in the outer carton to protect from light.
- If made at the bedside, the infusion must be administered immediately after preparation and remaining vial content discarded.
- If made in an aseptic environment, the prepared infusion solution may be stored at 2–8°C for 24 hours prior to administration. Ensure the solution is labelled appropriately.

## Dose[1,4,5]

Adult patients

Recommended dose is 8 mg/kg as a **SINGLE** intravenous infusion over 60 minutes (**maximum dose of 800 mg**).

*If appropriate round the dose to the nearest vial size to minimise wastage.* Note that the National COVID-19 Clinical Evidence Taskforce recommends flat doses based on weight ranges in-line with dosing in the RECOVERY trial. These dosing recommendations that can be found here.

Children and adolescents (< 16 years of age)

| Age range/weight | Dose |
|---|---|
| Infant < 1 year | 12 mg/kg |
| < 30 kg | 12 mg/kg |
| ≥ 30 kg | 8 mg/kg, maximum of 800 mg |

## Preparation and administration[4,10,11,12]

### Preparation of vials

The occupational hazard of intermittent low dose exposure to tocilizumab is not known. To minimise exposure, gloves and surgical mask should be worn when preparing this medication. Please refer to local protocol or guidelines on this matter. **Serious hypersensitivity reactions including anaphylaxis may occur. Resuscitation facilities must be readily available.**

### Dilution

1) Confirm the tocilizumab dose (mg) to be given to the patient and the equivalent volume (mL) of tocilizumab solution required from the vial(s).
2) **If the patient weighs 30 kg or more:**
   Using aseptic technique, withdraw this same volume from a **100 mL** sodium chloride 0.9% infusion bag, and discard **OR**
   **If the patient weighs less than 30 kg:**
   Using aseptic technique, withdraw this same volume from a **50 mL** sodium chloride 0.9% infusion bag, and discard
3) Withdraw the required tocilizumab dose from vial(s) and add to the sodium chloride 0.9% infusion bag.
4) To mix the solution, gently invert the bag to avoid foaming. Do NOT shake.
5) Inspect the bag to make sure it is clear to opalescent, colourless to pale yellow and free from visible particles, prior to administration.

### Administration^

1) Infuse intravenously over 60 minutes via a dedicated IV line. Do not use the same IV line to administer other medications at the same time.

**^**For adult patients, an initial slower infusion rate may be used to reduce the potential for infusion-related reactions. The NHS recommends 10 mL/hour for first 15 minutes then 130 mL/hour for the remaining 45 minutes, followed by a 20 mL sodium chloride 0.9% flush.

## Monitoring requirements[4,7,10]

- Observe for hypersensitivity reaction during, and for 30 minutes after IV infusion.
- Monitor for infusion related reactions and adverse effects including signs of infection, gastrointestinal symptoms suggestive of perforation, changes to neutrophil, platelet count and hepatic transaminases. Promptly investigate symptoms of hepatotoxicity such as jaundice, dark urine, itch, loss of appetite, nausea or vomiting.

## Adverse effects[4,10,13]

*Adverse effects in COVID-19 patients taking tocilizumab – clinical trial information included in updated Actemra® Product Information (December 2021)*

- The most common adverse reactions in COVID-19 patients (>1%) were increases in hepatic transaminases, constipation, diarrhoea, nausea, urinary tract infection, hypertension, hypokalaemia, anxiety, and insomnia.
- The rate of infection in COVID-19 patients taking tocilizumab alone, or with corticosteroids, was comparable to patients in the placebo arm.
- The incidence of laboratory abnormalities was generally similar between patients with COVID-19 who received one or two doses of tocilizumab compared to placebo groups. Decreases in platelets and neutrophils and elevations of ALT and AST were more frequent among patients receiving tocilizumab versus placebo.

*General adverse effect information*

- **Common (≥ 1% to < 10%):** Infections (including opportunistic), neutropenia, hypofibrinogenaemia, increased liver enzymes, gastritis, mouth ulcers, hypertension, infusion-related reactions (below), antibodies to tocilizumab, rash, itch, headache, dizziness.
- **Infrequent (0.1 – < 1%):** GI perforation (possibly dose-related), thrombocytopenia, hypersensitivity reactions (e.g. urticaria, angioedema), dyspnoea, cough, conjunctivitis.
- **Rare (< 0.1%):** Serious hepatotoxicity (including acute liver failure, hepatitis and jaundice, in some rare cases treatment has required liver transplant), pancreatitis, pulmonary fibrosis.

Infusion-related reactions: Occur within 24 hours of IV infusion; they include hypertension, headache, rash, hypersensitivity (anaphylaxis 0.2%).

## Reporting

- Suspected adverse events should be reported to the TGA, Roche (drug sponsor) and through the local incident reporting system. As approval for use of tocilizumab for COVID-19 is provisional, it is important to document and report all suspected adverse effects experienced by the patient during treatment to inform its long-term safety profile and future use.
- Drug and Therapeutics Committee oversight in the access process will enable appropriate medicines governance and ensure the collection and analysis of patient outcomes and systematic monitoring of medicine use. Tocilizumab use and outcome reporting should occur as per local governance processes.

## Summary of major changes made in version 2.4 – July 2022

- Tocilizumab global shortage resolved – removal of advice that baricitinib to be used in preference

## References

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