


| | | | | | | | |
|--|-----------|---|---|--------------|----|--|--|
| Parenteral Drug Therapy Manual  | IV ROUTES | | | OTHER ROUTES | | GENERIC NAME OF MEDICATION Tocilizumab | |
| | | D | C | I | SC | IM | OTHER NAMES ACTEMRA® |
| | RN | | Y | | | | CLASSIFICATION ASHP Immunomodulator, Monoclonal antibody |
| | RPN | | Y | | | | |
| MD | | Y | | | | | |

INDICATIONS

- **COVID-19 treatment is recommended for moderately to critically ill adults (at least 18 years of age) with with suspected or confirmed COVID-19 pneumonia who are on optimal concomitant steroids according to the following eligibility criteria (based on Provincial COVID-19 Guidelines):**
 - **Critically ill:** ICU-based patients requiring ventilator and/or circulatory support including high-flow nasal oxygen, CPAP, non-invasive ventilation, or mechanical ventilation; **AND** are on optimal dexamethasone therapy; **AND** are within 14 days of hospital admission.
 - **Moderately ill:** Ward-based patients with a C-reactive protein level of at least 75 mg/L **AND** have evidence of disease progression (i.e. increasing oxygen or ventilatory requirements) despite 24-48 hours of optimal dexamethasone therapy; **AND** are within 14 days of hospital admission.
 - **IMPORTANT:** Ordering of tocilizumab for COVID-19 treatment is **restricted to Infectious Diseases and Critical Care physicians. Two of these physicians are required to agree on tocilizumab treatment for a patient prior to initiation of therapy. Infectious Diseases physician must be one of the approvers when available. If Infectious Diseases physician unavailable, two Critical Care physicians may order. Note, treatment will be delayed until second approval is received and documented in patient chart.**
 - Please also refer to **Tocilizumab exclusion criteria below** for COVID-19 indication.
 - Tocilizumab will be stored in Critical Care.
- Treatment of adult patients with moderate to severe active rheumatoid arthritis (IV and SC formulations).
- Treatment of giant cell arteritis (GCA) in adults (SC formulation only).
- Treatment of active systemic juvenile idiopathic arthritis (SJIA) in children 2 years of age and older, who had an inadequate response to NSAIDs and systemic corticosteroids (IV and SC formulations).
- Treatment of polyarticular juvenile idiopathic arthritis (PJIA) in children 2 years of age and older who had an inadequate response to previous therapy with DMARDs (IV and SC formulations).
- Treatment of severe cytokine release syndrome (CRS) secondary to treatment with blinatumomab or with chimeric antigen receptor (CAR) T-cell therapy (e.g., tisagenlecleucel) in adults and children 3 years of age and older (IV formulation only).

ADMINISTRATION

- **There are 2 formulations: one for IV use (vial) and one for SC use (prefilled syringe and autoinjector). Ensure using the correct one.**
- Intermittent IV infusion: from a 100 mL NS solution bag (50 mL NS if patient weighs less than 30 kg), withdraw and discard the exact same volume of solution as the volume of tocilizumab to be added to the bag. Using the IV formulation, add tocilizumab slowly into the bag to get a final volume of exactly 100 mL (50 mL if patient weighs less than 30 kg). Gently mix by inverting the bag slowly to avoid foaming. Allow bag to reach room temp prior to infusion. Administer over 60 minutes. For COVID-19 Indication: The infusion speed recommended to be 10 mls per hour for 15 minutes and then increased to 130 mls per hour for the next 45 minutes. After completion of the infusion, at least 20 mls of 0.9% saline should be used to flush the drug through the giving set.
- SC: ensure using the SC formulation; allow the prefilled syringe or autoinjector to reach room temp. Inject SC the full amount in the syringe (162 mg/0.9 mL) into abdomen, thigh or upper arm; rotate injection sites. Ensure site of injection is free of moles, scars and open sores and is not tender, bruised, red or hard.

POTENTIAL ADMINISTRATION HAZARDS

- Hypersensitivity: anaphylactoid reactions, anaphylaxis.
- Infusion-related reactions: occur during or within 24 hours of infusion; hypertension, headache, dizziness, skin reactions (rash, pruritus, urticaria).
- GI: nausea, vomiting, diarrhea, dyspepsia, abdominal pain, mouth ulceration; gastrointestinal perforation, especially in patients with prior ulcers or diverticulitis.

- Endocrine and metabolic: elevation of lipids (total cholesterol, triglycerides, Low-Density-Lipoprotein cholesterol).
 - Hematologic: reduction in neutrophil count and platelet count.
 - Hepatic: elevation of liver enzymes (AST, ALT), acute liver failure.
 - Immunosuppression with increased risk of infections (bacterial, viral, fungal); more frequent in the elderly.
 - Local reactions: erythema, pruritus, pain and hematoma at SC injection sites.
- **Exclusion Criteria for COVID-19 Off-label Indication:**
 - **Known hypersensitivity to Tocilizumab**
 - **Non-COVID confirmed co-existing infection such as latent or active TB, fungal infections, Hepatitis B, etc.**
 - **Baseline AST or ALT greater than 5 x ULN**
 - **Baseline platelets less than 50**
 - **ANC less than 2**
 - **Pre-existing condition requiring ongoing pharmacological immunosuppression**
 - **Admitted for more than 14 days with COVID-19 signs and symptoms (or greater than 14 days of new COVID-19 diagnosis if nosocomially acquired)**

DOSAGE

Adults:

- **COVID-19 dosing using IV tocilizumab (to use IV formulation) for adults at least 18 years of age:**
 - **Weight-based dose banding strategy (800 mg if weight >90 kg; 600 mg if weight >65 kg and ≤90 kg; 400 mg if weight >40 kg and ≤65 kg; and 8mg/kg if weight ≤40 kg) for single dose.**
- Rheumatoid arthritis using IV tocilizumab (to use IV formulation):
 - Initial dose: 4 mg/kg IV every 4 weeks; may increase to 8 mg/kg based on clinical response.
 - For patients weighing more than 100 kg, do not exceed 800 mg/dose.
- Rheumatoid arthritis using SC tocilizumab (to use SC formulation):
 - If patient weighs less than 100 kg: 162 mg SC every other week, followed by an increase to every week based on clinical response.
 - If patient weighs 100 kg or more: 162 mg SC every week.
- Rheumatoid arthritis switching from IV to SC administration: give the first SC dose at the time of the next scheduled IV dose.
- GCA using SC tocilizumab (to use SC formulation): 162 mg SC every week (with a tapering course of corticosteroids); may be decreased to 162 mg SC every other week (with a tapering course of corticosteroids) based on clinical considerations.
- CRS using IV tocilizumab (to use IV formulation): 8 mg/kg (maximum of 800 mg/dose) IV. May administer up to 3 additional doses; dosing intervals may differ between protocols.

Pediatrics:

- SJIA using IV tocilizumab (to use IV formulation):
 - If patient weighs less than 30 kg: 12 mg/kg IV every 2 weeks.
 - If patient weighs 30 kg or more: 8 mg/kg IV every 2 weeks.
- SJIA using tocilizumab (to use SC formulation):
 - If patient weighs less than 30 kg: 162 mg SC every 2 weeks.
 - If patient weighs 30 kg or more: 162 mg SC every week.
- PJIA using IV tocilizumab (to use IV formulation):
 - If patient weighs less than 30 kg: 10 mg/kg IV every 4 weeks.
 - If patient weighs 30 kg or more: 8 mg/kg IV every 4 weeks.
- PJIA using SC tocilizumab (to use SC formulation):
 - If patient weighs less than 30 kg: 162 mg SC every 3 weeks.
 - If patient weighs 30 kg or more: 162 mg SC every 2 weeks.
- CRS using IV tocilizumab (to use IV formulation):
 - If patient weighs less than 30 kg: 12 mg/kg IV.
 - If patient weighs 30 kg or more: 8 mg/kg IV (maximum of 800 mg/dose).
 - May administer up to 3 additional doses; dosing interval may differ between protocols.

Adults and pediatrics:

- Dosage in renal impairment: no dosage adjustment needed in mild renal impairment; has not been studied in patients with moderate to severe renal impairment. For adult COVID-19 indication: dose adjustment not required.
- Dosage in hepatic impairment: not recommended. For adult COVID-19 indication: do not use if LFTs greater than 5 x ULN.
- Dosage adjustment due to toxicity: refer to manufacturer's recommendations.

COMPATIBILITY, STABILITY

(Consult NAPRA compounding standards; information provided below refers to physical/chemical stability and not to sterility)

- Store vials, prefilled syringes and autoinjectors between 2-8°C. Protect from light and freezing.
- Diluted IV solution is colourless to a pale yellow.
- The diluted IV solution is stable for 24 hours in the fridge and at room temp (up to 30°C) in NS in a PVC, polyethylene, polypropylene or glass container.
- The prefilled syringe and the autoinjector for SC administration are stable for 8 hours at room temp (below 30°C).

MISCELLANEOUS

- Tocilizumab should not be used with other biologic DMARDs (e.g., abatacept, adalimumab, anakinra, etanercept, infliximab, rituximab) because of possible increased risk of immunosuppression and infections.
- It would be prudent not to use tocilizumab in patients on azathioprine or cyclophosphamide.
- Use with caution if ANC is less than $2 \times 10^9/L$, platelet count less than $100 \times 10^9/L$, or AST or ALT exceeds 1.5 times the upper limit of normal. **(Please refer to COVID-19 Exclusion Criteria above)**
- Live and live attenuated vaccines should not be given concurrently with tocilizumab.
- Patients should be evaluated for tuberculosis risk factors and tested for latent and active infection before initiating therapy if feasible.
- Use with caution in patients with preexisting or recent onset CNS demyelinating disorders.
- If patient being treated with tocilizumab plus steroids and are at moderate to high risk for strongyloides infection, consider Infectious Diseases consult (if not done already) to assess if screening and/or pre-emptive treatment required.
- **Please note that COVID-19 tocilizumab recommendations are based on the Ontario COVID-19 Drugs and Biologics Clinical Practice Guidelines Working Group (on behalf of the Ontario COVID-19 Science Advisory Table) and the Ontario ICU Medication Task Force and are based on best available data to date and may change as additional data becomes available.**

REFERENCES

Ontario COVID-19 Drugs and Biologics Clinical Practice Guidelines Working Group on behalf of the Ontario COVID-19 Science Table (<https://covid19-sciencetable.ca/sciencebrief/clinical-practice-guideline-summary-recommended-drugs-and-biologics-in-adult-patients-with-covid-19/>)

Health Canada Tocilizumab (Actemra®) Product Monograph (2020)

Ottawa Tocilizumab PDTM (2020)

Provincial ICU Medication Task Force: Tocilizumab Eligibility and Exclusion Criteria (February 23, 2021)

REMAP-CAP Trial: <https://www.nejm.org/doi/full/10.1056/NEJMoa2100433>

RECOVERY Trial: <https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1>