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

**INDICATIONS**

- **COVID-19 treatment is recommended for moderately and critically ill adults (at least 18 years of age) 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:** hospitalized patients requiring ventilatory and/or circulatory support including high-flow nasal cannula, higher concentrations of oxygen by mask, CPAP, non-invasive ventilation, or invasive mechanical ventilation; **AND** are on optimal dexamethasone therapy; **AND** are within 14 days of hospital admission (or within 14 days of a new COVID-19 diagnosis if nosocomially acquired); **AND** have no exclusion criteria (see below).
    - **Moderately ill:** hospitalized patients requiring low-flow supplemental oxygen 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 (or within 14 days of a new COVID-19 diagnosis if nosocomially required); **AND** have no exclusion criteria (see below).
    - Note: Tocilizumab is not recommended outside of clinical trials for patients who are mildly ill with suspected or confirmed COVID-19 (non-hospitalized or hospitalized patients who do not require supplemental oxygen).
    - **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.**
- 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 (single use vials of 80mg/4mL; 200mg/10mL; 400mg/20mL) 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. 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), hypothyroidism.
- Hematologic: reduction in neutrophil count and platelet count, leukopenia.
- Hepatic: elevation of liver enzymes (AST, ALT) and bilirubin, acute liver failure.
- Immunosuppression with increased risk of infections (bacterial, viral, fungal) including upper respiratory tract infections and serious infections (tuberculosis, disseminated fungal infections, opportunistic infections); 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.**
  - **AST or ALT greater than 5 x ULN**
  - **Platelets less than 50 x$10^9$/L**
  - **ANC less than 2 x$10^9$/L**
  - **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 using actual body weight (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. Recommend to prepare just prior to administration.
- Do not infuse concomitantly in the same intravenous line with other drugs as compatibility unknown (run on own).
- 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 x $10^9$/L, platelet count less than 100 x$10^9$/L, or AST or ALT exceeds 1.5 times the upper limit of normal. **(Please refer to COVID-19 specific 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. (Consider CATMAT guidelines: https://www.canada.ca/content/dam/phac-aspc/migration/phac-aspc/publicat/ccdr-rmtc/16vol42/dr-rm42-1/assets/pdf/16vol42_1_ar-03-eng.pdf)**
- Other COVID-19 Indication Monitoring Considerations:
    - Baseline (if clinically relevant, feasible, and time permits): Hepatitis B surface antigen, LFTs, lipids, CBC
    - Ongoing: infusion-related reactions, CBC, new onset infection, abdominal symptoms, LFTs (if re-dosing)
- **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 Tocilizimub (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
Sunnybrook Health Sciences Centre IV Drug Monograph: Tocilizumab (March 3, 2021)
CATMAT statement on disseminated strongyloidiasis: Prevention, assessment and management guidelines (2016): https://www.canada.ca/content/dam/phac-aspc/migration/phac-aspc/publicat/ccdr-rmtc/16vol42/dr-rm42-1/assets/pdf/16vol42_1_ar-03-eng.pdf
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