Tocilizumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody that acts as an interleukin 6 (IL-6) receptor antagonist and is approved for the use of CAR-T associated cytokine release syndrome. Due to similarities in the clinical presentation of CAR-T cytokine release syndrome and the hyperinflammatory state of severe COVID-19, interest in tocilizumab for severe COVID-19 developed early in the pandemic. To a lesser extent, other IL-6 agents have also been investigated (e.g. sarilumab). Although several observational studies have suggested mortality benefit, data from randomized controlled trials to date have primarily shown no benefit from IL-6 antagonists. Emerging data from the REMAP-CAP, EMPACTA, and RECOVERY trials indicate positive benefits especially in critically ill patients.

Several agencies have published guidelines and/or position statements:

Per IDSA guidelines:
- Among hospitalized adults with progressive severe (SpO2 ≤94% on room air, including patients on supplemental oxygen) or critical COVID-19 (patients on mechanical ventilation, ECMO, or with end organ dysfunction as is seen in sepsis/septic shock (e.g. ARDS)) who have elevated markers of systemic inflammation (i.e. CRP ≥ 75 mg/L), the IDSA guideline panel suggests tocilizumab in addition to standard of care (i.e. steroids) rather than standard of care alone. (Last updated February 17, 2021).
  - Patients, particularly those who respond to steroids alone, who put a high value on avoiding possible adverse events of tocilizumab and a low value on the uncertain mortality reduction, would reasonably decline tocilizumab.

NIH COVID-19 Treatment Panel:
- For patients who are within 24 hours of admission to the intensive care unit (ICU) and require invasive or noninvasive mechanical ventilation or high-flow oxygen (>0.4 FiO2/30 L/min oxygen flow), there are insufficient data to recommend either for or against the use of tocilizumab or sarilumab for the treatment of COVID-19 (Last updated February 3, 2021).
  - Some Panel members would administer a single dose of tocilizumab (8 mg/kg of actual body weight, up to 800 mg) in addition to dexamethasone to patients who meet the above criteria and who are also exhibiting rapid progression of respiratory failure.
  - For patients who do not require ICU-level care or are admitted to the ICU but do not meet the above criteria, the Panel recommends against the use of tocilizumab or sarilumab for the treatment of COVID-19, except in a clinical trial (BIIa).

NHS Interim Guidance:
- Eligible patients include COVID positive/highly suspected patients who are receiving (or have completed a course of) dexamethasone or an equivalent corticosteroids AND with a C-reactive protein level of at least 75mg/L; AND an oxygen saturation of <92% on room air OR requirement for supplemental oxygen; OR If an IL-6 inhibitor has not been already administered for COVID-19 during this admission and within 24-48 hours of commencement of respiratory support (e.g. high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation). (Last updated February 22, 2021).
Sutter Health Patient Selection Criteria (start date – on or after March 10th, 2021)

Sutter Health has developed guidelines for the use of tocilizumab. Since there is no data to support safety and efficacy in pediatric patients, **there will be NO administration in adolescents at this time.**

- Hospitalized adult patients with confirmed COVID-19 AND
  - Oxygen saturation <92% on room air **OR**
  - Require supplemental oxygen AND evidence of systemic inflammation (i.e. CRP ≥ 75 mg/L) **OR**
  - Exhibiting rapid progression of respiratory failure AND within 24 hours of commencing respiratory support (e.g. high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation)

**Patient Exclusion**

Evidence of active TB or other non-COVID infection (bacterial, fungal, or viral), presumption of imminent death, condition or treatment resulting in ongoing immunosuppression including neutropenia (ANC <500), pregnancy, active liver disease or ALT/AST >5 x ULN, PLT< 50.
Prescriber Ordering

Tocilizumab

- An order panel "[tocilizumab (ACTEMRA) custom IVPB with COVID-19 Inclusion/Exclusion Criteria]" has been developed to aid with accurate ordering and documenting the requirements for use. This panel can be accessed via the larger COVID-19 Medications & Labs Order Panel.

- The use of tocilizumab in COVID-19 is off-label. Based on clinical trial data, the recommended dose of tocilizumab is 8 mg/kg to be administered as a single intravenous infusion over at least 1 hour. The total dose should not exceed 800 mg. A standardized dosing strategy is recommended based on the results of the RECOVERY trial:
  - Tocilizumab is one dose: 800 mg if weight >90kg; 600 mg if weight >65 and ≤90 kg; 400 mg if weight >40 and ≤65 kg; or 8 mg/kg if weight ≤40 kg.

- A second dose should not be considered, given the uncertainty over evidence of additional benefit as well as the need to maximize available supply.

- Tocilizumab must be given concomitantly with dexamethasone treatment. Tocilizumab monotherapy is not recommended and should not be considered as an alternative to corticosteroids.
Lab Test Results

<table>
<thead>
<tr>
<th>Component</th>
<th>Time Elapsed</th>
<th>Value</th>
<th>Range</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-Reactive Protein</td>
<td>1 day (03/02/21 0000)</td>
<td>70</td>
<td>MG/DL</td>
<td>In process</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>4 minutes (03/02/21 1132)</td>
<td>60 (A)</td>
<td>150 - 400 K/UL</td>
<td>In process</td>
</tr>
<tr>
<td>AST</td>
<td>1 day (03/02/21 0000)</td>
<td>43 (A)</td>
<td>0 - 37 U/L</td>
<td>In process</td>
</tr>
<tr>
<td>ALT</td>
<td>1 day (03/02/21 0000)</td>
<td>70 (A)</td>
<td>15 - 65 U/L</td>
<td>In process</td>
</tr>
</tbody>
</table>

Dose:
- **Administer Dose**: 600 mg
- **Administer Amount**: 600 mg

**Dose Calculation**
- 4 mg/kg/dose
- 8 mg/kg/dose

Diluent:
- NaCl 0.9%
- **Volume**: 0 mL

**Route**: Intravenous

**Frequency**:
- **Starting**: 3/3/2021
- **Q28 Days (0900)**
- **Admin. Inst.**:
  - For COVID-19 patients weighing greater than 65 kg to 90 kg. Infuse using a dedicated IV line. Do not infuse other agents through same IV....
- Refrigerate or store at room temperature. Allow solution to reach room temperature prior to administration. Protect from light.

**Administer**
- **Minutes**: 60

**Reference Links**
1. Lexi-comp
2. BLACK BOX WARNING

**Is patient confirmed to be infected with COVID-19 (SARS-CoV-2)?**
- Yes
- No

**Is patient confirmed to NOT be pregnant?**
- Yes
- No

**Is patient without evidence of – active tuberculosis, history of TB, or confirmed non-COVID infection (bacterial, fungal, viral)?**
- Yes
- No

**Is patient without evidence of – active liver disease or ALT/AST > 5 X ULN, ongoing immunosuppression or neutropenia (ANC <500), or PLT <50k**
- Yes
- No

**Note to Pharmacy**: + Add Note to Pharmacy (F6)
**Adverse Events and Monitoring**

**Tocilizumab**
Patients treated with tocilizumab are at increased risk for developing serious infections including TB, bacterial, invasive fungal, viral, or other opportunistic infections. Risks and benefits of treatment should be carefully considered prior to use of tocilizumab in patients with a history of recurring or chronic infections or with underlying conditions which may predispose patients to infections. Testing for latent TB should be considered prior to initiating tocilizumab but should not result in a delay of therapy. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with tocilizumab.

Other adverse reactions associated with tocilizumab include the risk of gastrointestinal perforation primarily as complications of diverticulitis, hepatotoxicity, laboratory abnormalities (i.e. neutropenia, thrombocytopenia, LFT elevation, and lipid abnormalities), and immunosuppression. Hypersensitivity including anaphylaxis and infusion related reactions have also been reported.

**Monitoring**
- Patient should be monitored for at least 1 hour after completion of infusion.
- Signs and symptoms of infusion related reactions include headache, nausea, dizziness, and hypotension. If infusion related reactions occur, immediately stop the infusion and notify the provider. The provider should immediately assess the patient and consider providing medications and supportive care for infusion reaction as necessary.

**Error and Adverse Event Reporting**
To date, no IL-6 inhibitor is FDA-approved or authorized for the treatment of COVID-19. Any serious suspected adverse reactions should be submitted online via [http://www.fda.gov.medwatch/report.htm](http://www.fda.gov.medwatch/report.htm)
For Pharmacists:

Order Verification
Prior to verifying a COVID-19 tocilizumab order, confirm that the patient meets inclusion criteria and does not meet any exclusion criteria described above. Pharmacists should provide any necessary administration information to nursing when applicable.

Product Availability and Admixing

Tocilizumab

- Tocilizumab is available in 20 mg/ml single-dose, preservative-free vials for further dilution prior to administration (80 mg/4ml, 200 mg/10ml, or 400 mg/20 ml)
- **For adult patients at or above 30 kg:**
  - From a 0.9% Sodium Chloride for Injection 100 mL infusion bag, withdraw and discard equivalent volume of saline equal to the volume of tocilizumab required for the patient’s dose (total volume 100 ml). For example, remove 20 ml normal saline from bag if using tocilizumab 400 mg/20 ml dose, 30 ml if using tocilizumab 600 mg/30 ml dose, or 40 ml if using tocilizumab 800 mg/40 ml dose
  - Withdraw the amount of tocilizumab from vial(s) using aseptic technique and transfer the content into the 0.9% Sodium Chloride Injection infusion bag (final volume of 100 ml). Gently invert IV bag by hand approximately 10 times to mix and avoid foaming. Do not shake. Discard any product remaining in the vials.
- **For adult patients less than 30 kg:**
  - From a 0.9% Sodium Chloride for Injection 50 mL infusion bag, withdraw and discard equivalent volume of saline equal to the volume of tocilizumab required for the patient’s dose (total volume 50 ml). For example, remove 10 ml normal saline from bag if using tocilizumab 200 mg/10 ml dose
  - Withdraw the amount of tocilizumab from vial(s) using aseptic technique and transfer the content into the 0.9% Sodium Chloride Injection infusion bag (final volume of 50 ml). Gently invert IV bag by hand approximately 10 times to mix. Do not shake. Discard any product remaining in the vials.

- Tocilizumab should be administered over 1 hour using a dedicated IV line and should not be infused concomitantly in the same IV line with other medications.
- Do not administer tocilizumab as an IV push or IV bolus.
- Tocilizumab should be discarded and not used if opaque particles or discoloration are visible.

Product Storage and Documentation

Tocilizumab

- Store unopened vials in the original carton to protect the vials from light and at a temperature of 2°C to 8°C (36°F to 46°F). Do not freeze.
- The admixed product can be stored between 2°C to 8°C (36°F to 46°F) for up to 24 hours and at room temperature for up to 4 hours, including infusion time and should be protected from light.
- If refrigerated, allow diluted tocilizumab to reach room temperature prior to infusion.
- Individual pharmacies may require staff to confirm completion of all required steps prior to dispensing tocilizumab, either via electronic I-Vent or paper documentation.
# TABLE 1: Tocilizumab Therapy At A Glance

<table>
<thead>
<tr>
<th><strong>Tocilizumab (Actemra®)</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IL-6 Inhibitor</strong></td>
<td>Tocilizumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody that acts as an interleukin 6 (IL-6) receptor antagonist and is approved for the use of CAR-T associated cytokine release syndrome. The use of tocilizumab in COVID-19 is off-label.</td>
</tr>
</tbody>
</table>
| **DOSE** | One-time dose based on weight, only for use in combination with dexamethasone (concurrently or course already completed):  
  - If > 90 kg = 800 mg  
  - >65 to 90 kg = 600 mg  
  - >40 to 65 kg = 400 mg  
  - ≤ 40 kg = 8 mg/kg |
| **VOLUME/DURATION** |  
  - Final volume 100 mL (if weight ≥ 30 kg) or 50 ml (if weight < 30 kg)  
  - Infuse over 60 minutes |
| **POTENTIAL BENEFIT** | When used in combination with dexamethasone, tocilizumab has demonstrated mortality benefit in patients with hypoxia or those requiring supplemental oxygen with evidence of systemic inflammation (i.e. CRP ≥ 75 mg/L). In addition, early use of tocilizumab (within 24 hours of commencing respiratory support) may improve clinical outcomes including survival among critically ill patients. |
| **STABILITY OF ADMIXED PRODUCT** | 24 hours refrigerated or 4 hours at room temperature |
| **SUPPLY** | Currently available |
| **SH PATIENT SELECTION CRITERIA (AS OF 3/3/2021)** | Hospitalized adult patients with confirmed COVID-19 AND  
  - Oxygen saturation <92% on room air **OR**  
  - Require supplemental oxygen AND evidence of systemic inflammation (i.e. CRP ≥ 75 mg/L) **OR**  
  - Exhibiting rapid progression of respiratory failure AND within 24 hours of commencing respiratory support (e.g. high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation) |
| **ADVERSE EVENTS** |  
  - Patients treated with tocilizumab are at increased risk for developing serious infections including TB, bacterial, invasive fungal, viral, or other opportunistic infections  
  - Potential for infusion related events and hypersensitivity reactions  
  - Observe patient for 1 hour post infusion |