**FORMULARY MONOGRAPH**

**Tocilizumab (Actemra®)**
[Genentech]

## REQUEST
- No formal request has been made to date for formulary review

## THERAPEUTIC USE
- Drug Class: Interleukin 6 (IL-6) receptor antagonist
- Population Served: Adults ≥ 18 years of age

## BACKGROUND
The mortality rate of severe COVID-19 has widely varied depending on the country and the institution providing care. With progression of the pandemic, more recent reports of COVID-19 ICU admissions have had an associated mortality rate near 40%, which is still higher than ICU admissions for other viral pneumonias.[2] Accumulating evidence suggests that the severity of COVID-19 is associated with elevated concentrations of inflammatory markers including cytokines, also referred to as cytokine release syndrome (CRS). Among these cytokines, elevated interleukin-6 (IL-6) is highly correlated to mortality.[3]

Tocilizumab is an IL-6 receptor monoclonal antibody that is FDA approved for CRS due to chimeric antigen receptor-T cell therapy (CAR-T). Due to similarities in the clinical presentation of CRS due to CAR-T and CRS due to severe COVID-19, tocilizumab has been a drug of interest since early in the pandemic and has numerous associated studies. Other IL-6 agents have been investigated, but not to the same extent as tocilizumab.[4]

Considering more recent studies investigating tocilizumab in COVID-19, updated IDSA guidelines are recommending tocilizumab be added to standard of care in hospitalized adults with progressive severe or critical COVID-19 who have elevated markers of systemic inflammation.[5] In addition, NIH treatment guidelines for COVID-19 recommend the use of tocilizumab in combination with dexamethasone in patients within 24 hours of admission to the ICU and who require invasive or noninvasive mechanical ventilation or high-flow oxygen or in recently hospitalized patients (not in an ICU) with rapidly increasing oxygen needs who require noninvasive or high-flow oxygen and have significantly elected markers of inflammation.[6]

## CLINICAL PHARMACOLOGY & MECHANISM OF ACTION[7]
Tocilizumab is an antagonist of the interleukin-6 (IL-6) receptor. Endogenous IL-6 is induced by inflammatory stimuli and mediates a variety of immunological responses. Inhibition of IL-6 receptors by tocilizumab leads to a reduction in cytokine and acute phase reactant production.

## *FDA APPROVED INDICATIONS[7]
- Cytokine release syndrome (CRS) due to chimeric antigen receptor-T cell therapy in patients ≥ 2 years of age, severe of life-threatening– August 2017
- Giant cell arteritis (GCA) in adults– May 2017
- Polyarticular juvenile rheumatoid arthritis (PJRA) in patients ≥ 2 years of age – April 2013
- Systemic onset juvenile chronic arthritis (SJIA) in patients ≥ 2 years of age– April 2011
- Rheumatoid arthritis (RA) in adults, moderate to severe– September 2008

***POTENTIAL UNLABELED USE/OFF LABEL USE[7]**

- COVID-19 treatment – Level of Evidence [G]
- Cytokine release syndrome due to bi-specific T-cell engaging therapy, severe of life-threatening– Level of Evidence [C]

**PROCUREMENT & STORAGE[7]**

| Formulation | Availability | Storage | Stability |
|---|---|---|---|
| Intravenous solution | 80 mg/4 mL (4 mL vial); 200 mg/10 mL (10 mL vial); 400 mg/20 mL vial (20 mL vial) | Store intact vials at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect vials, from light (store in the original package until time of use). | Solutions diluted for IV infusion in NS may be stored at 2°C to 8°C (36°F to 46°F) or room temperature for up to 24 hours; protect from light.<br>Solutions diluted for IV infusion in 1/2 NS may be stored at 2°C to 8°C (36°F to 46°F) for up to 24 hours or at room temperature for up to 4 hours; protect from light. |
| Subcutaneous auto-injector solution | Not utilized for COVID-19 indication. | | |
| Subcutaneous prefilled syringes | Not utilized for COVID-19 indication. | | |

**HAZARDOUS CLASSIFICATION**

This drug is not on the National Institute for Occupational Safety and Health (NIOSH) or Resource Conservation and Recovery Act (RCRA) list as a hazardous drug.

**DOSAGE & ADMINISTRATION[7,10]**

| Indication | Route | Adult Dosing | Notes |
|---|---|---|---|
| COVID-19 (see guideline recommendations above) | Intravenous | 8 mg/kg of actual body weight as a single dose (maximum dose: 800 mg) infused over 60 minutes; may consider a second dose 12-24 hours later | No subcutaneous dosing for this indication.<br>Generally recommended in combination with steroids. |

| Order Build Elements: | IT Build Notes (use N/A where necessary): |
|---|---|
| Name and strength of all units needing to be built for dispensation | Actemra (tocilizumab) IV solution<br>- 80 mg/4 mL (4 mL)<br>- 200 mg/10 mL (10 mL)<br>- 400 mg/20 mL (20 mL) |
| Default Dose | N/A |
| Dose Buttons | 280 mg, 400 mg, 600 mg, 800 mg, 1000 mg (based on weight) |
| How should doses be rounded? | N/A |
| Default Route | Intravenous infusion |
| Route Buttons | Intravenous infusion |
| Default Frequency | Once |
| Frequency Buttons | Doses, Days |

| | |
|---|---|
| PRN Reasons | N/A |
| Default Duration | N/A |
| Duration Buttons | 60 minutes |
| Comments- Pharmacy notes | N/A |
| MAR Administration Instructions | N/A |
| Order Instructions | N/A |
| Label Comments | N/A |

**IV GUIDELINE MONOGRAPH TEMPLATE[9]**

| | |
|---|---|
| **DRUG** | Actemra (tocilizumab) |
| **APPROVED NURSING AREA(s)** | All |
| **IV PUSH (Yes/No)** | No |
| **INTERMITTENT INFUSION (Yes/No)** | Yes |
| **CONTINUOUS INFUSION (Yes/No)** | No |
| **INFUSION PUMP REQUIRED (Yes/No)** | No |
| **REFERENCE** | Package Insert |
| **ADDITIONAL INFORMATION** | Allow diluted solution to reach room temperature prior to administration. Infuse over 60 minutes. Do not infuse other agents through the same IV line. Do not use if opaque particles or discoloration is visible. |

**IV PREPARATION INSTRUCTIONS[9]**

Patients < 30 kg: use a 50 mL infusion bag or bottle of 0.9% or 0.45% Sodium Chloride Injection
Patients ≥ 30 kg: use a 100 mL infusion bag or bottle of 0.9% or 0.45% Sodium Chloride Injection

Step 1. Withdraw a volume of Sodium Chloride Injection, USP, equal to the volume of the tocilizumab injection required for the patient's dose from the infusion bag or bottle
Step 2. Withdraw the amount of tocilizumab for intravenous infusion from the vial(s) and add slowly into the 0.9% or 0.45% Sodium Chloride Injection, USP infusion bag or bottle. To mix the solution, gently invert the bag to avoid foaming. Diluted solutions are compatible with polypropylene, polyethylene, polyvinyl chloride, and glass infusion containers.

**PHARMACOKINETICS[7]**

| | |
|---|---|
| **Metabolism** | Antibodies primarily undergo catabolism |
| **Bioavailability** | 100% |
| **Elimination** | Combination of linear and nonlinear clearance; linear clearance ranges from 5.7 mL/hr to 12.5 ml/hr depending on studied indication |
| **Half-life (t 1/2)** | Ranges from 11 to 17 days depending on the studied indication |

**PHARMACOKINETICS IN SPECIAL POPULATIONS[7]**

| Special Population | Considerations |
|---|---|
| **Gender (females)** | • No specific gender considerations |
| **Elderly - age > 65 years** | • No dose adjustments provided; the frequency of serious infection is higher in elderly patients |

| | |
|---|---|
| **Pediatric - age <18 years** | • Only adults included in COVID-19 studies<br>• Safe and effective in children ≥ 2 years of age with PJIA, SJIA and CRS; dosing is available for those indications |
| **Renal Impairment** | • No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab have been conducted<br>- CrCl ≥30 mL/minute: no dosage adjustment necessary<br>- CrCl <30 mL/minute: no dosage adjustments provided; however, based on tocilizumab's molecular weight, it is unlikely to be significantly renally eliminated |
| **Hepatic Impairment (Moderate Impairment)** | • No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab have been conducted<br>- Initiation of therapy: baseline ALT or AST >1.5 × ULN is not recommended<br>- During therapy (not as applicable to COVID-19 due to single dose administration):<br>- Baseline ALT or AST >1 to 3 × ULN (persistent): reduce dose to 4 mg/kg or interrupt until ALT/AST have normalized<br>- Baseline ALT or AST >3 to 5 × ULN (confirmed with repeat testing): interrupt until ALT/AST <3 × ULN and follow dosage adjustments recommended >1 to 3 × ULN; for persistent increases >3 × ULN, discontinue<br>- Baseline ALT or AST >5 × ULN: discontinue |

**PREGNANCY SUMMARY & USE IN BREAST FEEDING[7]**

**Pregnancy**

- Monoclonal antibodies are transported across the placenta during third trimester
- Outcome information specific to use in pregnancy for COVID-19 is limited. The risk of severe illness from COVID-19 infection is increased in pregnant patients. Pregnancy is a high-risk medical condition as defined by the Centers for Disease Control and Prevention. Refer to current guidelines for the treatment of pregnant patients.
- Tocilizumab is currently under investigation for use in the treatment of COVID-19. Health care providers are encouraged to enroll patients exposed to COVID-19 during pregnancy in the Organization of Teratology Information Specialists pregnancy registry or the PRIORITY (Pregnancy CoRonavIrus Outcomes RegIsTrY).

**Lactation**

- Tocilizumab is present in human milk and according to the manufacturer, the decision to continue or discontinue breastfeeding during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.

***ADVERSE DRUG EVENTS / EFFECTS[8]**

**Common >10 %:**

- Increased serum cholesterol (19% - 20%; children and adolescents: ≤2%)

- Increased serum alanine aminotransferase (≤36%), increased serum aspartate aminotransferase (≤22%)
- Injection site reaction (SubQ: children and adolescents: 15% - 44%; adults: 4% - 10%)
- Infusion-related reaction (4% - 20%)
- Neutropenia (children and adolescents <30 kg: 26%)

**Moderate risk 1 – 10%:**
- Cardiovascular: Hypertension (1% to 6%), peripheral edema (<2%)
- Central nervous system: Headache (1% to 7%), dizziness (3%)
- Dermatologic: Skin rash (2%)
- Endocrine & metabolic: Increased LDL cholesterol (9% to 10%; children and adolescents ≤2%), hypothyroidism (<2%)
- Gastrointestinal: Diarrhea (children and adolescents: ≤5%), abdominal pain (2%), oral mucosa ulcer (2%), gastric ulcer (<2%), stomatitis (<2%), weight gain (<2%), gastritis (1%)
- Hematologic & oncologic: Neutropenia (adults: 2% to 7%; children ≥30 kg: 4%), thrombocytopenia (1% to 2%), leukopenia (<2%)
- Hepatic: Increased serum bilirubin (<2%)
- Immunologic: Antibody development (children and adolescents: ≤6%; adults: <2%)
- Infection: Herpes simplex infection (<2%)
- Ophthalmic: Conjunctivitis (<2%)
- Renal: Nephrolithiasis (<2%)
- Respiratory: Upper respiratory tract infection (7%), nasopharyngitis (7%), bronchitis (3%), cough (<2%), dyspnea (<2%)

**Rare risk <1 %:**
- Active tuberculosis, anaphylaxis, angioedema, aspergillosis, candidiasis, cellulitis, chronic inflammatory demyelinating polyneuropathy, cryptococcosis, diverticulitis, gastroenteritis, gastrointestinal perforation, hepatic failure, hepatic injury, hepatitis, hepatotoxicity, hypertriglyceridemia, hypotension, increased HDL cholesterol, jaundice, malignant neoplasm, multiple sclerosis, nausea, opportunistic infection, pancreatitis, pneumonia, septic arthritis, sepsis, Stevens-Johnson syndrome, urinary tract infection, viral infection

**CONTRAINDICATIONS**[7]
Hypersensitivity to tocilizumab

**MEDICATION SAFETY ASSESSMENT & RECOMMENDATIONS**[9]
- **Black box Warnings**:
  - Patients treated with tocilizumab are at increased risk for infections, some progressing to serious infections leading to hospitalization or death. These infections have included bacterial infection, tuberculosis, invasive fungal or other opportunistic infections. Evaluate for latent tuberculosis and treat, if necessary, prior to initiation of therapy. Monitor patients receiving tocilizumab for signs and symptoms of infection. If a serious infection develops, interrupt tocilizumab until the infection is controlled.
- ***Sentinel Events Advisories posted:** No
- **High Alert/SALAD:** Tocilizumab may be confused with sarilumab
- **Dual Sign/Witness:** N/A
- **Monitoring (not as applicable to COVID-19 due to single dose administration):**
  - Latent TB screening prior to therapy initiation

- Neutrophils, platelets (prior to therapy, 4 to 8 weeks after start of therapy, and every 3 months thereafter [RA, GCA])
- ALT/AST, alkaline phosphatase, and total bilirubin (prior to therapy, every 4 to 8 weeks after start of therapy for the first 6 months, and every 3 months thereafter [RA, GCA])
- Lipid panel (prior to therapy and 4 to 8 weeks following initiation of therapy, then subsequently according to current guidelines)

- ***Significant Drug Interactions:**
  - CYP3A4 substrates: May decrease concentrations of substrates – monitor therapy
  - Anti-TNF agents: May enhance immunosuppressive effects– avoid combination
  - Other DMARDs: May enhance immunosuppressive effects– avoid combination
  - Tacrolimus: May enhance immunosuppressive effects– avoid combination
  - COVID-19 Vaccine: May diminish the effect of vaccine
    - Defer COVID-19 vaccination for at least 90 days after receipt of monoclonal antibodies
  - Live Vaccines: May diminish the effect of vaccine
    - Administer live vaccines at least 3 months after receipt of immunosuppressant therapy, unless benefit outweighs risk
    - Defer immunosuppressant therapy for at least 4 weeks after administration of live vaccines
  - Inactivated Vaccines: May diminish the effect of vaccine
    - Administer inactivated vaccines at least 3 months after receipt of immunosuppressant therapy
    - Defer immunosuppressant therapy for at least 2 weeks after administration of inactivated vaccines
- **REMS requirements:** None
- **Warnings/Precautions (monitoring not as applicable to COVID-19 due to single dose administration):**
  - GI perforation: Use with caution in patients at increased risk for GI perforation; perforation has been reported, typically secondary to diverticulitis.
  - Hematologic effects: Neutropenia and thrombocytopenia may occur; may require treatment interruption, dose or interval modification, or discontinuation.
    - Monitor neutrophils and platelets. Do not initiate treatment in patients with an ANC <2,000/mm3 or platelet count <100,000/mm3; discontinue treatment for ANC <500/mm3 or platelet count <50,000/mm3.
  - Hepatic effects: Hepatic injury, resulting in liver transplant or death, has been reported. May occur months to years after treatment initiation and may present with marked elevations of hepatic transaminases or signs or symptoms of hepatic dysfunction with mildly elevated transaminases. May require treatment interruption, modification, or discontinuation.
    - Monitor LFTs prior to therapy initiation and during treatment.
    - It is not recommended to initiate treatment in patients with baseline ALT or AST >1.5 × ULN; discontinue treatment for ALT or AST >5 × ULN.
  - Herpes zoster reactivation: Herpes zoster reactivation has been reported.
  - Hyperlipidemia: Reported increases in total cholesterol, triglycerides, LDL, and/or HDL
    - Monitor ~4 to 8 weeks after initiation, then according to current guidelines.
  - Hypersensitivity: May cause hypersensitivity or anaphylaxis; anaphylactic events including fatalities have been reported with IV administration; hypersensitivity reactions have occurred in patients who were pre-medicated
    - Medications for the treatment of hypersensitivity reactions should be available for immediate use.

- Malignancy: May affect defenses against malignancies, though impact is not fully defined; however, malignancies were observed in clinical trials.
- Demyelinating CNS disease: Use with caution in patients with preexisting or recent onset CNS demyelinating disorders; rare cases of CNS demyelinating disorders (multiple sclerosis and chronic inflammatory demyelinating polyneuropathy) have occurred.

- ***Potential for Errors and Abuse:** None
- ***Other Risks:** None

**SIMILAR PRODUCTS BY CLASS or TREATMENT INDICATION**

| Available Products | Class | Indication | Notes |
|---|---|---|---|
| Sarilumab (Kevzara®) | Interleukin 6 (IL-6) receptor antagonist | Off-label use for COVID-19 treatment | Less extensive research compared to tocilizumab. IDSA guidelines have no recommendations for sarilumab, whereas the NIH recommends against use of sarilumab outside of a clinical trial.[5,6] |

***THERAPEUTIC EFFECTIVENESS**

| RECOVERY (Preliminary) Horby, et al. (Feb 2021)[10] | |
|---|---|
| **Objective** | - Randomized, controlled, open-label platform trial in the UK to evaluate the effects of potential treatments in hospitalized COVID-19 adult patients |
| **Eligibility** | - Adults with suspected or confirmed COVID-19, O2 less than 92% on room air or on supplemental oxygen, and a CRP ≥75 mg/L |
| **Study Arms** | - Tocilizumab plus standard of care (SOC) (N=2022)<br>  - 800 mg if >90kg; 600 mg if >65 and ≤90 kg; 400 mg if >40 and ≤65 kg; and 8mg/kg if ≤40 kg; a second dose could be given 12 to 24 hours later<br>- Standard of care alone (N=2094) |
| **Primary Endpoint** | - All-cause mortality within 28 days of randomization |
| **Outcomes** | - Groups similar at baseline; median CRP of 143 mg/dL, 14% mechanically ventilated, 41% had non-invasive respiratory support, and 82% on steroids<br>- Median time from hospitalization to randomization: 2 days (IQR 1-5 days)<br>- Median days since symptom onset in tocilizumab vs SOC was 9 days (IQR 7-13 days) vs 10 days (IQR 7-14 days)<br>- Lower 28-day mortality with tocilizumab (29.5%) vs. standard of care (33.1%) (RR 0.86, CI 0.77-0.96); for those on steroids, tocilizumab (27%) vs. SOC (33%) (RR 0.80, CI 0.70-0.90); no significant difference for those not on steroids<br>- 54% in the tocilizumab group and 47% in the SOC group were discharged within 28 days (RR 1.22, CI 1.12-1.34)<br>- Initiation of mechanical ventilation or death was lower with tocilizumab (33%) vs. SOC (38%) (RR 0.85, CI 0.78-0.93)<br>- Three reports of serious adverse reactions potentially related to tocilizumab, including otitis externa, Staphylococcus aureus bacteremia, and lung abscess, all of which resolved with standard treatment |
| **Limitations[4]** | - Preliminary report<br>- Trial is open-label design, which could introduce bias<br>- 17% of patients allocated to the tocilizumab group did not receive the drug |

| | |
|---|---|
| | - Included patients without a confirmed SARS-CoV-2 PCR; however, a subgroup analysis of patients with PCR (94%) found similar results<br>- Mortality rate in this study is higher than general findings in hospitalized COVID-19 patients in the US<br>- Given mortality of hospitalized patients has declined over time, it would be helpful to assess if the mortality difference seen in this study holds when examining only patients from later in the study period |
| **REMAP-CAP Gordon, et al. (Jan 2021)[11]** | |
| **Objective** | - Randomized, controlled, open-label, platform trial in the UK to evaluate the effect of tocilizumab/sarilumab on survival and organ support in critically ill COVID-19 adult patients |
| **Eligibility** | - ICU adults with suspected or confirmed COVID-19 within 24 hours of respiratory (NIV, HFNC, MV) or cardiovascular organ support initiation |
| **Study Arms** | - Tocilizumab plus standard of care (N=353)<br>  - 8 mg/kg of actual body weight; max of 800 mg; a second dose could be given 12 to 24 hours later<br>- Sarilumab (400 mg) plus standard of care (N=48)<br>- Standard of care alone (N=402) |
| **Primary Endpoint** | - Respiratory and cardiovascular organ support-free days (up to day 21) |
| **Outcomes** | - Groups similar at baseline; 29% mechanically ventilated, 42% had non-invasive respiratory support, and 93% on steroids<br>- Median time from hospitalization to randomization was 1.5 days (IQR 0.8-2.8 days)<br>- Median organ support-free days were 10, 11, and 0 for tocilizumab, sarilumab, and control, respectively; relative to control, median adjusted OR were 1.64 (CI 1.25-2.14) for tocilizumab and 1.76 (CI 1.17-2.91) for sarilumab, yielding >99.9% and 99.5% probability of superiority<br>- Mortality was 28% for tocilizumab, 22% for sarilumab, and 36% for control; relative to control, median adjusted OR were 1.64 (CI 1.14-2.35) for tocilizumab and 2.01 (CI 1.18-4.71) for sarilumab, yielding 99.6% and 99.5% probability of superiority<br>- Treatment effect was greater in combination with steroids than either intervention on its own<br>- Nine serious adverse events potentially related to tocilizumab, including one secondary bacterial infection, five bleeds, and two cardiac events; there were none in the sarilumab group. |
| **Limitations[4]** | - Trial is open-label design, which could introduce bias<br>- Included patients without a confirmed SARS-CoV-2 PCR<br>- Some data is missing (11 outcomes) and some patients remain hospitalized, so long-term outcomes may differ from the short-term outcomes presented here |

| Summary of Tocilizumab RCTs[10] | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Study** | **Severity** | **Tocilizumab Mortality** (Duration of follow-up) | **Control Mortality** (Duration of follow-up) | **Steroid Use** | **Time from Symptom Onset** | **NIMV or IMV**** | **Comments** |
| **RCT-TCZ-COVID-19 N=126** | Severe | 3.3% [2/60] (30 day) | 1.6% [1/63] (30 day) | 9.8% | 8 (6-11) | 0% | Open label, underpowered |
| **CORIMUNO-TOCI-1 N=131** | Moderate-severe | 11.1% [7/63] (28 day) | 11.9% [8/67] (28 day) | 33% vs. 61% | 10 (7-13) | 0% | Open label |
| **BACC Bay N=243** | Severe-critically ill | 5.6% [9/161] (28 day) | 3.8% [3/81] (28 day) | 9.5% | 9 (6-13) | 4% | Potentially underpowered |
| **COVACTA N=438** | Severe | 19.7% [58/294] (28 day) | 19.4% [28/144] (28 day) | 36.1% vs. 54.9% | 11 vs. 10 (no IQR) | 69% | Median days until hospital discharge: 20d in tocilizumab arm vs. 28d in SOC arm (HR 1.35, CI 1.02-1.79) |
| **EMPACTA N=377** | Severe | 10.4% [26/249] (28 day) | 8.6% [11/128] (28 day) | 82.8% | 8 (no IQR) | 27% | Mechanical ventilation or death: 12% in tocilizumab arm vs. 19.3% in SOC arm (P=0.04) |
| **TOCIBRAS N=129** | Severe-critically ill | 21.5% [14/65] (28 day) | 9.4% [6/64] (28 day) | 83.6% vs. 88.7% | 10 vs. 9.5 (no IQR) | 48% | Open label, underpowered; Death at day 15: 17% in tocilizumab arm vs. 3% in SOC arm (OR 6.42, CI 1.59-43.2) |
| **REMAP-CAP N=755** | Critically ill | 28.0% [98/350] (In-hospital) | 35.5% [142/397] (In-hospital) | 85% | Unk; < 24 hrs organ support | 100% | Open label; see therapeutic effectiveness table |
| **RECOVERY N=4,116** | Severe-critically ill | 29.5% [596/2022] (28 day) | 33.1% [694/2094] (28 day) | 82% | 9 (7-13) vs. 10 (7-14) | 55% | Open label; see therapeutic effectiveness table |
| **All RCTs** | | **24.8%** | **27.5%** | **OR 0.87 (0.79-0.96)** | | | |

Green = statistically significant; red= not statistically significant

**non-invasive mechanical ventilation or invasive mechanical ventilation

## VALUE ANALYSIS/ FINANCIAL ANALYSIS OF COST OF THERPAY

| Actemra Formulation | NDC | Vendor | Inpatient infusion (per unit) | Inpatient AWP (per unit) |
|---|---|---|---|---|
| 80mg/4mL (4 mL vial) | 50242-0135-01 | Morris & Dickson | $461.16 | $553.39 |
| 200mg/10mL (10 mL vial) | 50242-0136-01 | Morris & Dickson | $1152.90 | $1383.50 |
| 400mg/20mL (20 mL vial) | 50242-0137-01 | Morris & Dickson | $2305.80 | $2767.00 |

**OVERALL SUMMARY AND RECOMMENDATION**

Prior to the publication of the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) and Randomized Evaluation of COVID-19 Therapy (RECOVERY) trials, conflicting data was available regarding the clinical benefits of tocilizumab in the treatment of COVID-19.[10,11] To date, REMAP-CAP and RECOVERY are the two largest clinical trials of IL-6 inhibitors and have demonstrated a statistically significant mortality benefit in the studied patient population. Although the mortality benefits was appear clinically modest, the findings prompted both the IDSA and NIH to advocate for the addition of tocilizumab to the standard of care in hospitalized adults with progressive severe or critical COVID-19 who have elevated markers of systemic inflammation.[5,6] It should be noted that the use of corticosteroids was high (>80%) in both studies, and Horby et al. found that the overall significant mortality benefit of tocilizumab was retained in patients receiving concomitant corticosteroids but not in those without concomitant corticosteroids.[10] Similarly, Gordon and colleagues found the treatment effect of tocilizumab was greater when used in combination with corticosteroids. In addition to decreased mortality with the use of tocilizumab, Gordon et al. noted improvement in median organ support-free days and Horby et al. found a reduced composite of initiation of mechanical ventilation or death.[10,11]

When comparing REMAP-CAP and RECOVERY to previously published trials, it is important to note that these previous studies had lower rates of corticosteroid use and fewer patients with a need for non-invasive respiratory support or mechanical ventilation, which likely lead to the conflicting results published. In addition, several previous trials were underpowered. One consistent result across all trials to date was that there has been no increase in rates of serious adverse events reported compared to standard of care, and overall, these rates have been low.

While the recently shown mortality benefit and low risk for serious adverse events make tocilizumab an appealing option for the treatment of COVID-19, institutional cost is a potential limiting factor. Based on an adult weight of 70-100 kg, the cost of a single dose of tocilizumab would range from $3,458 to $4,612. While a single dose is the typical treatment regimen, Gordon et al found a second dose being administered, at the discretion of the physician, in 29% of patients.[11]

Based on the above considerations, we recommend maintaining tocilizumab, for the off-label use of COVID-19 treatment, as a non-formulary agent in order to ensure it is reserved for patients meeting all the following criteria:

- Confirmed COVID-19
- CRP > 7.5mg/dL
- Within 48 hours of commencement of respiratory support (high flow nasal oxygen, CPAP, non-invasive ventilation, ECMO, or invasive mechanical ventilation)
- Received or concurrently receiving corticosteroids (unless contraindicated)

Exclude if:

- AST/ALT > 10 x ULN
- Significant immunosuppression, particularly in those with a history of recent use of other biologic immunomodulating drugs
- An uncontrolled, serious bacterial, fungal, or non-SARS-CoV-2 viral infection
- Absolute neutrophil count <500 cells/µL
- Platelet count <50,000 cells/µL

Treatment courses will be limited to a single dose, based on actual body weight and rounded to the nearest vial size. At this time, the data is insufficient to support a second dose of tocilizumab and is not recommended.

- >90 kg: 800 mg
- >65 and ≤90 kg: 600 mg
- >40 and ≤65 kg: 400 mg
- ≤40 kg: 8mg/kg

**MONOGRAPH PREPARED BY AND DATE**

Julia McElyea/Jessica Ortwine/Wenjing Wei/Norman Mang – March 2021
Kelly Slaten– February 2021
*****The Joint Commission Requirements MM.02.01.01 & CMS §482.25(b)(9) (must be completed for each new drug addition)
MM.02.01.01

EP2. The hospital develops and approves criteria for selecting medications, which, at a minimum, include the following: - Indications for use - Effectiveness - Drug interactions - Potential for errors and abuse - Adverse drug events - Sentinel event advisories - Population(s) served (for example, pediatrics, geriatrics) - Other risks – Costs. The hospital determines a method to monitor the response of the patient.

Interpretive Guidelines §482.25(b)(9)

The medical staff must establish a formulary system. The formulary lists medications for dispensing or administration that the hospital maintains or that are readily available. In accordance with accepted standards of practice, the medical staff, in consultation with the pharmacy service, should develop written criteria for determining what medications are available for dispensing or administration. At a minimum, the criteria include the indication for use, effectiveness, risks (including propensity for medication errors, abuse potential, and sentinel events), and costs.

Processes and mechanisms should be established to monitor patient responses to a newly added medication before the medication is made available for dispensing or administration within the hospital.

**REFERENCES**


1. Rahim F, Amin S, Noor M, et al. Mortality of patients with severe COVID-19 in the intensive care unit: an observational study from a major COVID-19 receiving hospital. Cureus. 2020;12(10):e10906.
2. Armstrong R, Kane A, Cook T. Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies. Anaesthesia. 2020;75(10):1340-9.
3. Hojyo S, Uchida M, Tanaka K, et al. How COVID-19 induces cytokine storm with high mortality. Inflamm Regen. 2020;40:37.
4. CDC and IDSA. Tocilizumab/IL-6 Inhibitors. *COVID-19 Real Time Learning Network.* Last updated: February 17, 2021. Accessed: February 24, 2021. https://www.idsociety.org/covid-19-real-time-learning-network/therapeutics-and-interventions/Tocilizumab-IL-6-Inhibitors/
5. Bhimraj A, Morgan R, Shumaker A, et al. IDSA Guidelines on the Treatment and Management of Patients with COVID-19. *Infectious Disease Society of America.* Last updated: February 22, 2021. Accessed: February 24, 2021. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

6. NIH. The COVID-19 Treatment Guidelines Panel's Statement on the Use of Tocilizumab (and Other Interleukin-6 Inhibitors) for the Treatment of COVID-19. *COVID-19 Treatment Guidelines.* Last updated: March 5, 2021. Accessed: March 10, 2021. https://www.covid19treatmentguidelines.nih.gov/statement-on-tocilizumab/
7. Tocilizumab. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Hudson, OH. Available at: http://online.lexi.com. Accessed: February 25, 2021.
8. Genentech Inc (2010). Actemra (Tocilizumab) - Highlights of prescribing information. [Package insert] Genentech Inc. San Francisco, CA
9. Tocilizumab. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Available at: http://www.micromedexsolutions.com. Accessed on October 24, 2019.
10. Horby P, 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 2021.02.11.21249248
11. Gordon A, Mouncey P, Al-Beigh F, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. N Engl J Med. 2021. [Epub ahead of print]