Treatment Plan for COVID-19 in Adults at CMH Using Actemra (Tocilizumab)

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of Actemra (tocilizumab) for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. Actemra is FDA-approved for several indications, however, it is not approved for the treatment of COVID-19.

Based on the totality of scientific evidence available, the FDA has determined it is reasonable to believe that Actemra may be effective for the treatment of COVID-19 when used under the conditions described in the EUA, and that the known and potential benefits of Actemra outweigh the known and potential risks

Actemra is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of tocilizumab under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner

For the most up to date Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) for Actemra, and Fact Sheet for Patients, Parents and Caregivers: Emergency Use Authorization (EUA) of Actemra for Coronavirus Disease 2019 (COVID-19) please visit https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization

Purpose:
Define the criteria and provide guidance to providers for the use of Actemra at CMH for the treatment of COVID-19 in hospitalized patients.

Mechanism of Action:
Actemra is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass and binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. COVID-19-associated systemic inflammation and hypoxic respiratory failure can be associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin. It is hypothesized that modulating the levels of IL-6 or its effects may reduce the duration and/or severity of COVID-19 illness.

Approved Available Alternatives:
For the most up to date information to find if there is an adequate, approved and available alternative to Actemra information on treatments can be found at:

- https://www.cdc.gov/coronavirus/2019-ncov/index.html
- https://www.covid19treatmentguidelines.nih.gov/
- https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs

The health care provider should visit https://clinicaltrials.gov/ to determine whether the patient may be eligible for enrollment in a clinical trial.

Inclusion/Exclusion Criteria:

Inclusion criteria:

- Confirmed COVID-19 via laboratory testing (per EUA)
- Hospitalized Adult or pediatric patient (2 years of age and older) (per EUA)
- Receiving systemic corticosteroids (per EUA)
- Laboratory Parameters Checked: Use not recommended with an absolute neutrophil count (ANC) less than 1000 per uL, platelet count below 50,000 per uL, or ALT or AST above 10 times the upper limit of the reference range (per EUA)
- Require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO (Per EUA)
- Exhibiting rapid respiratory decompensation due to COVID-19
- Elevated markers of inflammation
- Requires Infectious disease approval for use

Exclusion criteria:

- See Warnings and Precautions
- Patients with known hypersensitivity to any ingredient of Actemra must not receive it. Actemra is formulated with a disodium phosphate dodecahydrate/sodium dihydrogen phosphate dihydrate buffered solution. Each mL of solution contains polysorbate 80 (0.5 mg), sucrose (50 mg), and Water for Injection, USP.

Use in Specific Populations

- Pregnancy: The limited available data with Actemra in pregnant women are not sufficient to determine whether there is a drug-associated risk for major birth defects and miscarriage. Actemra should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus
    - There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Actemra during pregnancy. Healthcare providers are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.
- Lactation: No information is available on the presence of tocilizumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production.
- Pediatric use: Pediatric use is supported by evidence justifying emergency use of Actemra for the treatment of COVID-19 in hospitalized adults as well as safety and dosing information of

Actemra in pediatric patients for other uses. Actemra is not authorized or approved for the emergency use for patients younger than 2 years of age.
    - It is recommended that there be a discussion with a Pediatric ID specialist before using. The outpatient on-call provider at Maine Medical Partners Pediatric Specialty Care can be reached at 207-662-5522
- Geriatric use: No dose adjustment is required in elderly patients >65 years of age
- Renal Impairment: No dose adjustment is required in patients with mild or moderate renal impairment
- Hepatic impairment: See Warnings and Precautions

Dosing:
- The dosing for emergency use of Actemra authorized under this EUA given as a single 60-minute intravenous infusion is:
    - Patients less than 30 kg weight: 12 mg/kg
    - Patients at or above 30 kg weight: 8 mg/kg
- Maximum dosage in COVID-19 patients is 800 mg per infusion
- If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of tocilizumab may be administered at least 8 hours after the initial infusion
- subcutaneous administration is not authorized for the treatment of COVID-19 patients

Potential Drug Interactions:
- Interactions with CYP450 Substrates: Inhibition of IL-6 may lead to increased metabolism of drugs that are CYP450 substrates. Caution should be exercised when co-administering Actemra with CYP3A4 substrate drugs where decrease in effectiveness is undesirable. The effect of Actemra on CYP450 enzyme activity may persist for several weeks after stopping therapy.

Monitoring Parameters:
- Laboratory monitoring: Monitor ALT, AST, neutrophils and platelet counts prior to therapy initiation and according to current standard clinical practice
- signs and symptoms of infection (prior to, during, and after therapy)
- signs and symptoms of CNS demyelinating disorders
- new onset abdominal symptoms
- Monitor for hypersensitivity reactions, including anaphylaxis

Adverse Reactions
- The adverse reaction rates observed in the clinical studies of Actemra used to support this EUA cannot be directly compared to rates in the clinical studies of Actemra for rheumatoid arthritis, giant cell arteritis, systemic sclerosis-associated interstitial lung disease, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, and cytokine release syndrome and may not reflect the rates observed in clinical practice.

- Most common adverse reactions (incidence ≥ 3%) are constipation, anxiety, diarrhea, insomnia, hypertension and nausea
- See Warnings and Precautions

Warnings and Precautions

- Serious Infections:
    - Actemra should not be administered if patients have any other concurrent active infection (other than COVID-19), including localized infection. Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including Actemra.
    - The risks and benefits of treatment should be considered prior to initiating Actemra in patients with chronic or recurrent infection, or who have a history of a serious or an opportunistic infection
    - Closely monitor patients for the development of signs and symptoms of infection during and after treatment, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants.
- Tuberculosis:
    - Tuberculosis (pulmonary or extrapulmonary) has been reported in patients receiving tocilizumab; both reactivation of latent infection and new infections have been reported.
- Gastrointestinal Perforation:
    - Events of gastrointestinal perforation have been reported in clinical trials for chronic indications, primarily as complications of diverticulitis, in patients treated with Actemra. Use with caution in patients who may be at increased risk for gastrointestinal perforation. Promptly evaluate patients presenting with new onset abdominal symptoms for early identification of gastrointestinal perforation.
- Immunosuppression:
    - Actemra should be avoided in patients who are significantly immunosuppressed, particularly in those with recent use of other biologic immunomodulating drugs
- Hepatotoxicity
    - During randomized, controlled studies, treatment with Actemra was associated with a higher incidence of transaminase elevations. Serious cases of hepatic injury have been observed in patients taking intravenous or subcutaneous Actemra chronically. In this setting, the time to onset for cases ranged from months to years after treatment initiation
    - The decision to administer Actemra should balance the potential benefit against the risks of acute treatment. Actemra is not recommended in COVID-19 patients with elevated ALT or AST above 10 times the upper limit of the reference range. When ACTEMRA is used for treatment of COVID-19, ALT and AST should be monitored according to current standard clinical practice

- Active hepatic disease and hepatic impairment
    - Actemra is not recommended in patients with active hepatic disease or hepatic impairment
- Laboratory Parameters:
    - In randomized, controlled trials, patients receiving Actemra had higher rates of neutropenia, thrombocytopenia, and elevations of ALT or AST.
    - ACTEMRA is not recommended in COVID-19 patients with an absolute neutrophil count (ANC) less than 1000 per mm^3, platelet count below 50,000 per mm^3, or ALT or AST above 10 times the upper limit of the reference range
    - Monitor ALT, AST, neutrophils and platelet counts according to current standard clinical practice
- Hypersensitivity Reactions, Including Anaphylaxis
    - Hypersensitivity reactions, including anaphylaxis, have been reported in association with Actemra and anaphylactic events with a fatal outcome have been reported with intravenous infusion of Actemra. These events have occurred both with and without previous hypersensitivity reactions and as early as the first infusion. If anaphylaxis or other hypersensitivity reaction occurs, stop administration immediately and discontinue Actemra permanently. Do not administer to patients with known hypersensitivity to Actemra
- Demyelinating Disorder
    - The impact of treatment with Actemra on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in rheumatoid arthritis clinical studies. Monitor patients for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of Actemra in patients with preexisting or recent onset demyelinating disorders
- Vaccinations:
    - Avoid use of live vaccines concurrently with Actemra as clinical safety has not been established.

Additional Physician Requirements:

- Healthcare provider **MUST:**
    - Receive approval for use from Infectious Disease
    - Obtain written consent using the CMH drug specific consent form
        - Copy to be faxed to pharmacy
    - Complete patient Inclusion/Exclusion Checklist
        - Copy to be faxed to pharmacy
    - Patient Counseling Information:
        - As a healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the “FACT SHEET FOR PATIENTS, PARENTS

AND CAREGIVERS"
(https://www.gene.com/download/pdf/actemra_eua_patient_fact_sheet.pdf)

- Provide them with a copy of this Fact Sheet prior to administration
  - However, if providing this information will delay the administration of to a degree that would endanger the life of a patient, the information must be provided to the parent and/or caregiver as soon as feasible after Actemra administration.

- Report of all serious adverse events and medication errors potentially related to Actemra within 7 calendar days from the onset of the event
  - See Reporting Section for additional information on how to report
- Provide mandatory responses to requests from FDA for information about adverse events and medication errors associated with Actemra

Reporting of Medication Errors and Serious Adverse Events:

- The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events and medication errors potentially related to Actemra within 7 calendar days from the onset of the event
- The prescribing health care provider and/or the provider's designee is/are to provide mandatory responses to requests from FDA for information about adverse events and medication errors associated with Actemra

Health care providers/ designee must submit a report on all of the following

What to Report	When to Report / To Whom	When to Report / To Whom
Medication errors	Within 48 hours of onset of the event to the Clinical Research Department	Within 7 calendar days from onset of the event to FDA and Genentech
Unexpected Adverse Events occurring during Actemra treatment (for example, diagnoses or findings that change the clinical care of the patient)	Within 48 hours of onset of the event to the Clinical Research Department	Within 7 calendar days from onset of the event to FDA and Genentech
Serious Adverse Events related to/potentially attributable to Actemra	Within 48 hours of onset of the event to the Clinical Research Department	Within 7 calendar days from onset of the event to FDA and Genentech
Deaths	Within 48 hours of onset of the event to the Clinical Research Department	Within 7 calendar days from onset of the event to FDA and Genentech

Serious Adverse Events are defined as:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- A medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly

Reports must be submitted to the FDA and Genentech. The Clinical Research Department can aid in this process.

(1) Email all of the following Clinical Research Department staff:
- Dr. Kathryn Rohr rohrka@cmhc.org
- Kylie Guy guyky@cmhc.org
- Jennifer Chase chaseje@cmhc.org

(2) Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:
- Complete and submit the report online: www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
- Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
- Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

(3) In addition, provide a copy of all FDA MedWatch forms to:
- Genentech US Drug Safety
- Fax: 1-650-238-6067 or 1-650-225-4630
- E-mail: us_drug.safety@gene.com or call Genentech at 1-888-835-2555 to report adverse events.

References:

- US Food and Drug Administration (FDA). Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) for Actemra (tocilizumab). https://www.fda.gov/media/150321/download Published June 24, 2021. Accessed June 25, 2021
- National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated July 8, 2021. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed July 29, 2021.
- Actemra (tocilizumab) [prescribing information]. South San Francisco, CA: Genentech Inc; March 2021.