



July 1, 2021

Tocilizumab (Actemra®) for Treatment of COVID-19 - EMERGENCY USE AUTHORIZATION -

Mechanism of action^{1,2,3,4}:

Tocilizumab is an interleukin-6 receptor (IL-6) antagonist, currently FDA-approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis, giant cell arteritis, polyarticular and systemic juvenile idiopathic arthritis, as well as cytokine release syndrome. Higher levels of IL-6 have been positively correlated with cases of critical and severe COVID-19, whereas lower levels of IL-6 have been correlated with mild disease; in addition, elevated levels of IL-6 have been found to be predictive of the likelihood of need for mechanical ventilation.

Current Status¹:

Tocilizumab is not FDA approved for the treatment of COVID-19. On June 24, 2021, the FDA issued an Emergency Use Authorization (EUA) to permit the emergency use of tocilizumab for treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) **who are receiving systemic corticosteroids and are requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).**

Availability:

Tocilizumab is commercially available through the IHS Pharmaceutical Prime Vendor, McKesson, and can be obtained by the IHS National Supply Service Center (NSSC) at no cost to I/T/U facilities for the management of COVID-19. Please contact the NSSC if interested in procuring tocilizumab for the treatment of COVID-19 in accordance with the EUA.

Efficacy^{2,4,5}:

Randomised Evaluation of COVID-19 Therapy (RECOVERY) (Currently unpublished)

<i>Design:</i>	Randomized, controlled, open-label, multi-center platform study conducted in the UK to evaluate the efficacy and safety of standard of care plus tocilizumab (n=2022) vs standard of care (n=2094) in hospitalized adult patients with severe COVID-19 pneumonia
<i>Patients:</i>	Mean age: 63.6 years, 14% invasive mechanical ventilation, 41% non-invasive ventilation or high-flow oxygen, 45% low flow oxygen; 82% receiving systemic corticosteroids
<i>1° outcome:</i>	Decreased risk of death through Day 28: 30.7% receiving tocilizumab vs. 34.9% standard of care (absolute risk reduction in death of 4%); HR 0.85 (95% CI 0.76 to 0.94, $p=0.0028$)
<i>2° outcome:</i>	Decreased time to hospital discharge: 19 days for tocilizumab vs. >28 days in standard of care; HR 1.22 (95% CI 1.12-1.33)
<i>2° outcome:</i>	Decreased new requirements for mechanical ventilation by Day 28: 35% tocilizumab vs. 42% standard of care; RR 0.84 (95% CI 0.77 to 0.92)

Tocilizumab in Patients Hospitalized with COVID-19 Pneumonia (EMPACTA)

<i>Design:</i>	Randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of intravenous tocilizumab in combination of standard of care (n=249) vs standard of care (n=128) in hospitalized, non-ventilated adult patients with COVID-19 pneumonia
<i>Patients:</i>	Median age: 57 years, 26.5% high-flow oxygen, 64.2% low flow oxygen; 72.7% systemic corticosteroids and 47.7% remdesivir
<i>1° outcome:</i>	Decreased need for mechanical ventilation or death (combined) by Day 28: 12% tocilizumab vs. 19.3% standard of care; HR 0.56 (95% CI 0.33-0.97, $p=0.04$)

Adverse Drug Events²:

The most common adverse reactions (incidence $\geq 3\%$) are constipation, anxiety, diarrhea, insomnia, and nausea. *Note:* Adverse events observed in clinical studies of tocilizumab used to support the EUA cannot be directly compared to rates in the clinical studies for rheumatoid arthritis or other approved conditions.

Warnings and Precautions²:

- **Serious infections (Boxed warning)** - tocilizumab should not be administered if patients have any other concurrent active infection, including localized infection.
- **Gastrointestinal perforation** - events have been reported in clinical trials for chronic indications in patients treated with tocilizumab. Use with caution in patients who may be at increased risk.
- **Hepatotoxicity** – tocilizumab is not recommended in patients with active hepatic disease, hepatic impairment, or with elevated ALT or AST above 10 times the upper limit of the reference range. Monitor ALT and AST according to current standard clinical practice.
- **Neutropenia and thrombocytopenia** – tocilizumab is not recommended in COVID-19 patients with an absolute neutrophil count (ANC) less than 1000 per mm³ or platelet count below 50,000 per mm³. Monitor neutrophils and platelet counts according to current standard clinical practice.
- **Hypersensitivity** – Hypersensitivity reactions including anaphylaxis have been reported with tocilizumab infusions.
- **Live Vaccinations** - Avoid the use of live vaccines with tocilizumab. The interval between live vaccinations and therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

Dosing²:

Tocilizumab is administered as an intravenous infusion. *Tocilizumab subcutaneous administration is not authorized for the treatment of COVID-19 patients.*

- Patients less than 30 kg weight: 12 mg/kg as a single 60-minute infusion (maximum dose 800mg)
- Patients at or above 30 kg weight: 8 mg/kg as a single 60-minute infusion (maximum dose 800mg)

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. No dose adjustment is required in patients >65 years of age or in patients with mild/moderate renal impairment.

Mandatory Requirements under the EUA^{2,6}:

1. Treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and are requiring supplemental oxygen, invasive mechanical ventilation, or ECMO.
2. As the healthcare provider, communicate to your patient or parent/caregiver information consistent with the “Fact Sheet for Patients, Parents and Caregivers” prior to the patient receiving tocilizumab. Healthcare providers (to the extent practicable given the circumstances of the emergency) must document in the patient’s medical record that the patient/caregiver has been:
 - a. Given the “[Fact Sheet for Patients, Parents and Caregivers](#)”,
 - b. Informed of alternatives to receiving authorized tocilizumab, and
 - c. Informed that tocilizumab is an approved drug that is authorized for the unapproved use under this EUA
3. Patients must have aminotransferases and CBC with differential determined prior to first administration of tocilizumab.
4. The prescribing healthcare provider and/or the provider’s designee are/is responsible for mandatory reporting of all medication errors and all serious adverse events and medication errors potentially related to tocilizumab treatment within 7 calendar days from onset of the event.
 - Should include the words “ACTEMRA treatment under EUA” in the “Describe Event” section
 - Should include the words “Indian Health Service” or “IHS” on the form in the reporter section (section G).
 - Information on the FDA MedWatch program can be found on the [IHS Pharmacovigilance website](#).

References:

1. U.S. Food and Drug Administration. [Letter of Authorization](#). Emergency Use Authorization (EUA) for tocilizumab.
2. U.S. Food and Drug Administration. [Fact Sheet for Healthcare Providers](#). Emergency Use Authorization (EUA) for tocilizumab.
3. ACTEMRA (tocilizumab). [PRODUCT INFORMATION](#). Chugai Seiyaku Kabushiki Kaisha Corp., Marketed by Genentech, Inc. San Francisco, CA 94080.
4. Salama C, Han J, Yau, L., et al. [Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia](#). *New England Journal of Medicine*, 2021; 384(1): 20–30.
5. U.S. National Library of Medicine. [ClinicalTrial.gov NCT04381936](#). Accessed June 30, 2021.
6. U.S. Food and Drug Administration. [Fact Sheet for Patients, Parents and Caregivers](#). Emergency Use Authorization for tocilizumab.