Tocilizumab (ACTEMRA) for COVID-19
Frequently Asked Questions (FAQ)
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

Background

The COVID-19 pandemic caused by a novel coronavirus has resulted in significant morbidity and mortality, and therapies are needed to treat severe infections due to this virus. Tocilizumab (TOCI) is an interleukin-6 inhibitor, approved for use in several rheumatologic conditions, including rheumatoid arthritis, and on June 24th, 2021, based on the results of clinical trials, it was granted an FDA Emergency Use Authorization (EUA), making it available for treatment of hospitalized patients with severe COVID-19. The EUA is based on the totality of evidence, which suggests it is reasonable to believe the known and potential benefits outweigh the known and potential risks when used as described in the EUA. This FAQ is designed to serve as a resource for VHA physicians, pharmacists, nurses, and other healthcare personnel on the use of tocilizumab in the management of severe COVID-19.

Tocilizumab: Mechanism of Action in COVID-19 and Pharmacokinetics

What is TOCI and how does it work as a treatment for COVID-19?

- Tocilizumab is a monoclonal antibody that binds to soluble and membrane bound human IL-6 receptors. TOCI is currently FDA approved for the treatment of several rheumatologic conditions, including rheumatoid arthritis, and giant cell arteritis. It also is approved for the treatment of severe cytokine release syndrome (CRS) associated with CAR-T cell therapy.[1]
    - CRS in response to CAR-T cells manifests a fever, encephalopathy, tachycardia, hypotension, coagulopathy and multi-organ dysfunction. Laboratory findings include elevated C-reactive protein, ferritin, tumor necrosis factor (TNF), interferon-ɣ and several interleukins, including IL-1 and IL-6.
    - Tocilizumab was FDA approved for severe or life-threatening CRS due to CAR-T cells based on 2 retrospective cohort series, showing resolution of CRS within 14 days of TOCI administration in 70% in one cohort and 53% in the other.[1,2]
- Early on in the COVID-19 pandemic, it was recognized that some cases of severe COVID-19 presented with a clinical syndrome similar to CRS, or cytokine storm, including respiratory failure with elevated levels inflammatory markers such as ferritin, d-dimer, IL-2 and IL-6, and that these markers were elevated with poor prognosis, leading to interest in and early case series of TOCI in COVID-19.[3,4,5]
- It is postulated that TOCI and other IL-6 inhibitors may exert a positive effect on COVID-19 through modulation of IL-6, and disruption of the cytokine storm seen in severe cases.
- At this time, the FDA EUA of TOCI in COVID-19 is based on 4 randomized controlled trials, RECOVERY, EMPACTA, COVACTA and REMDACTA.
    - **NOTE: *tocilizumab is NOT an FDA approved drug for the treatment of COVID-19, but is authorized for Emergency Use with a scope that is limited to patients meeting ALL criteria outlined in the EUA*.**
    - **TOCI is authorized for the treatment of COVID-19 in hospitalized patients with a positive SARS-CoV-2 direct viral test who are receiving systemic corticosteroids AND require supplemental oxygen, invasive or non-invasive mechanical ventilation or ECMO.**

What are the known Pharmacokinetic (PK) parameters of TOCI in COVID-19?

- Pharmacokinetic data in patients with COVID-19 is available from a population PK analysis of 380 adults treated with 8 mg/kg of TOCI intravenously with the following findings:[6]
    - Estimated median (range) C_{max} was 151 mcg/mL (78-319 mcg/mL)
        - Estimated median (range) C_{max} after 2 doses of 8 mg/kg separated by 8 hours was 290 mcg/mL (152-604 mcg/mL)
    - Estimated median (range) C_{day28} was 0.229 m cg/mL (0.00119-19.4 mcg/mL)
    - Estimated volume of distribution was 8.75 L
    - With the single dose, concentrations were below quantification after an average of 35 days with clearance dependent on COVID-19 severity, with consistent decreases of 13% for each increased severity ordinal score category

- Average linear CL 17.6 mL/hr in patients on supplemental oxygen
- Average linear CL 22.5 mL/hr in patients on high-flow oxygen or non-invasive ventilation
- Average linear CL 29 mL/hr in patients on mechanical ventilation
- Average linear CL 35.4 mL/hr in patients requiring ECMO or mechanical ventilation + additional organ support

- Additional PK data with intravenous TOCI is available in the prescribing information for TOCI for FDA approved uses.[1]
  - In patients with giant cell arteritis, no change in TOCI exposure was seen in patients with moderate renal impairment
  - No PK data is available in patients with hepatic impairment
- While TOCI does not have a direct impact on CYP enzymes, IL-6 does reduce mRNA expression of several isoenzymes, including CYP1A2, 2B6, 2C9/19, 2D6 and 3A4.[1,6] As a result, TOCI may blunt the effect by reducing IL-6, which could result in decreased exposure of drugs metabolized by those enzymes and patients should be watched for reduced efficacy for several weeks after an infusion. (e.g. warfarin, cyclosporine, tacrolimus, simvastatin, etc.)

Tocilizumab Dosing in COVID-19

- **The recommended dosage of TOCI for severe COVID-19 in adults is 8 mg/kg (to a max of 800 mg) for those weighing ≥ 30kg as a single intravenous infusion[6]**
  - One additional dose of 8 mg/kg can be administered at least 8 hours after the first if signs and symptoms of COVID-19 worsen or do not improve after the first dose
  - Subcutaneous administration is NOT authorized for the treatment of COVID-19 based on the FDA EUA
- **Preparation and Administration**
  - TOCI is supplied as 20 mg/mL single dose vials, in quantities of 80mg, 200mg and 400mg per vial.
  - The full dose of TOCI (8 mg/kg) should be added to a 100 mL prefilled bag of 0.9% or 0.45% sodium chloride, after withdrawing an amount equal to the TOCI from the prefilled bag (0.4 mL/kg)
  - Once diluted, the product may be stored for up to 24 hours refrigerated or up to 4 hours at room temperature and should be protected from light
  - The infusion should be administered over 60 minutes with an infusion set, and should not be infused concomitantly in the same intravenous line with other drugs.
- **Dose adjustments in special populations**
  - **Renal insufficiency:** Limited PK data in patients with moderate renal insufficiency do not show significant differences in exposure and no dose adjustment is needed in patients with renal insufficiency
  - **Hepatic impairment:** No formal data are available on the PK of TOCI in patients with hepatic impairment
  - **Body weight:** TOCI exposure in COVID-19 was affected by body weight, where patients weighing less than 60 kg had 20% lower exposure than those with a weight of at least 80 kg.
  - **Age:** no specific PK data exists in COVID-19, however similar effectiveness and safety was noted in patient age 65 years or older in randomized controlled trials of TOCI, including EMPACTA, COVACTA and REMDACTA (39% of patients receiving TOCI), and in those 70 years of age or older in RECOVERY (34% of patients receiving TOCI)

Tocilizumab Efficacy for COVID-19 Infections

What efficacy data currently exist for the use of TOCI as treatment of COVID-19 infections?

- **Clinical efficacy data:** The EUA approval of TOCI was based on analysis of a 4 randomized-controlled trials (RCT), and of those, one was an open-label arm of the RECOVERY platform comparing TOCI to patients receiving usual care, and 3 were randomized, double-blind, placebo-controlled trials (EMPACTA, COVACTA, and REMDACTA).[7-11] Two of the 4 trials showed a beneficial effect of TOCI on the primary outcome, while the other two did not, but provide supportive safety data. Table 1 provides a summary of the study design for the 4 main RCTs.
- In addition to the four trials referenced above, a number of other open-label randomized controlled trials have been published, with varying efficacy results. For more information on these additional trials, see Table 2.

Table 1: Study design of RCTs leading to EUA of TOCI for COVID-19

Study	Study design	Population	Treatments	Outcomes
RECOVERY[7]	Open-label, adaptive platform in UK. TOCI was a second randomization for select patients after a prior randomization to other therapy (e.g. antivirals, steroids)	Hospitalized patients with evidence of progression after primary randomization (O_2 saturation on room air < 92% or on supplemental O_2 and CRP ≥ 75 mg/L) Those with evidence of active infection ineligible	TOCI 400mg, 600mg or 800mg based on weight vs. usual care, 2nd dose could be given 12-24 hours later at investigator discretion if no improvement	**Primary:** Mortality through day 28 **Secondary:** time to hospital discharge, need for MV* in those not needed it at baseline **Safety:** cause-specific mortality, major arrhythmias
EMPACTA[8]	Double-blind, placebo-controlled RCT (2:1)	Hospitalized patients with O_2 saturation <94% on room air or on supp. O_2 but excluded those on NIV/MV**, active infection, AST/ALT> 5x ULN, ANC<1000/uL, Platelets<50K, immunocompromised or history of diverticulitis or GI perforation – *goal was to enroll more minorities*	TOCI 8 mg/kg (maximum 800mg) or placebo, with optional 2nd dose 8-24 hours later if the patient worsened	**Primary:** Composite need for MV or death by day 28 **Secondary:** time to hospital DC (or readiness), time to 2 category improvement in COVID-19 ordinal score, time to clinical failure, death **Safety:** incidence and severity of adverse events
COVACTA[9]	Double-blind, placebo-controlled RCT (2:1)	Hospitalized patients with severe COVID-19 (O_2 sat < 94% on room air or P/F^+ < 300 and infiltrates). Excluded patients with other suspected active infection, AST/ALT >10 x ULN, ANC<1000/uL, platelets < 50K	TOCI 8 mg/kg (maximum 800mg) or placebo, with optional 2nd dose 8-24 hours later if the patient worsened	**Primary:** clinical status at day 28 (based on ordinal scale) **Secondary:** Time to discharge, length of ICU stay, mortality, need for MV **Safety:** incidence of serious adverse events
REMDACTA[10]	Double-blind, placebo-controlled RCT (2:1)	Hospitalized patients with severe COVID-19 (needing > 6 L/min O_2 to maintain O_2 saturation > 93%), excluded other suspected active infection, immunosuppression, ANC<1000/mm^3, platelets<50,000/mm^3, eGFR< 30mL/min, AST/ALT > 5 X ULN	Remdesivir + TOCI 8 mg/kg (maximum 800mg) vs. remdesivir + placebo with optional seconde dose 8-24 hours later if the patient worsened	**Primary:** Time to hospital discharge or "ready for discharge" **Secondary:** mortality, need for MV/death, clinical status

**MV = mechanical ventilation, **NIV/MV = invasive or non-invasive ventilatory support $^+PF = PaO_2/FiO_2$*

Study Results for TOCI in COVID-19:

- **RECOVERY:**[7] The RECOVERY trial included 2022 patients who received TOCI + usual care and 2094 with usual care alone. Mean age was 63 years, 67% were male, and 76% were white. The duration of symptoms was 9 days in the TOCI arm and 10 days in the usual care arm and over half of the patients had comorbidities. Steroids were given to 82% of subjects in each group. The majority of patients were either receiving no ventilatory support other than oxygen (46% and 45% of TOCI and usual care) or non-invasive ventilation (41% of each group), with a small number on mechanical ventilation (13% and 14%, respectively).
    - **Mortality at 28 days was reduced with TOCI, 31% with TOCI vs 35% with usual care** (HR 0.85, 95% CI 0.76 to 0.94, p=0.0028). In addition, TOCI was associated with a significantly greater likelihood of discharge at day 28 (57% vs. 50%, p<0.0001), and in those not on invasive mechanical ventilation at baseline, the risk of progressing

to MV or death was also significantly lower (35% vs 42%, p<0.0001). The benefit was retained in those receiving corticosteroids, but not in those who did not (29% vs. 35% for those on corticosteroids – RR 0.79, 95% CI 0.7 to 0.89).

- *This is the largest RCT for the use of TOCI for COVID-19, but is a pragmatic trial, where TOCI was given as a second randomization after a primary therapy and was open-label. There was a suggestion that those on steroids may be more likely to derive benefit, although this is a subgroup analysis.*

➢ **EMPACTA:**[8] EMPACTA included 389 patients, 249 in the TOCI and 128 in the placebo arms. Median age was 57 years, 59% were male, and 53% were white, with a median symptom duration of 8 days. Corticosteroids were used in 73% of each group. At baseline, 64% of patients received low flow and 27% required high-flow O_2 supplementation. 48% of patients also received remdesivir.

- **By day 28, the proportion of patients who required mechanical ventilation or died was lower in those who received TOCI (12% vs 19%),** p=0.04, although mortality alone was not different (10.4% with TOCI vs 8.6% with placebo). No difference in most of the other secondary outcomes was noted.
- *This was a relatively large, blinded RCT, and did show a benefit on the composite endpoint in a fairly low-severity population, where most were on steroids, and nearly half also on remdesivir, but did not show a difference in mortality (which was low in both arms).*

➢ **COVACTA:**[9] COVACTA analyzed 294 patients who received TOCI vs. 144 who received placebo. Median age in this study was 62 years, 70% were male and 58% were white. A lower percentage of patients received glucocorticoids in the tocilizumab group than in the placebo group both *at baseline* (57 [19.4%] vs. 41 [28.5%]) (Table 1) and *during* the trial (99 [33.7%] vs. 75 [52.1%])TOCI and placebo patients respectively and the symptom duration was longer than other trials (11 vs. 10 days with TOCI and placebo). In contrast to previous trial, the majority of patients in the TOCI and placebo groups were on high-flow oxygen/non-invasive ventilation (32% and 27%), mechanical ventilation (15% and 10%) or ECMO (23% and 28%), indicating a sicker patient population.

- **No difference was seen in the primary outcome when looking at clinical status at day 28. In addition, most of the secondary endpoints also did not show a difference between TOCI and placebo**, including mortality at day 28 (19.7% vs 19.4%), although TOCI was associated with a reduced time to discharge (or ready to discharge) at 20 days vs. 28 days with placebo.
- *This relatively large, blinded RCT did not confirm the benefit seen in RECOVERY, or COVACTA in a high-severity population (with over a third in each arm on mechanical ventilation or ECMO). Patients had a longer symptom duration and received less corticosteroids than in RECOVERY and EMPACTA, and less patients received corticosteroids in the TOCI arm*

➢ **REMDACTA:**[10] Available data for the REMDACTA trial is limited to a press-release from Roche and has not been published in peer-reviewed form. REMDACTA included 430 patients treated with TOCI + remdesivir and 210 who received placebo + remdesivir. Median age in this study was 60 years, 63% were male and 67% were white. According to the TOCI EUA, the vast majority (80%) were on non-invasive ventilation or high-flow O_2 supplementation, with an additional 14% on invasive mechanical ventilation. The duration of symptoms was 8 days, and 84% of patients had received corticosteroids at baseline. Details on outcomes are scant, but according to the media announcement and the EUA, treatment with **TOCI + remdesivir failed to meet the primary endpoint of time to discharge (or ready for discharge) versus remdesivir and placebo through day 28 (HR 0.965, 95% CI 0.78 to 1.19)).** Additionally, no difference was seen in need for MV/death or death at 28 days (HR 0.98, 95% CI 0.72 to 1.34). Mortality at day 28 was 18.1% with TOCI + remdesivir and 19.5% with placebo + remdesivir (weighted difference -1.3%, 95% CI -7.8 to 5.2%).

- Like COVACTA, TOCI failed to show a beneficial impact on any outcome (over remdesivir alone), in the largest of the 3 blinded RCTs, in which a large majority received corticosteroids, and had a symptom duration of 8 days. Limited data is available to assess baseline differences between the groups or labs related to hyperinflammation.

➢ In addition to the 4 RCTs considered for the EUA Fact Sheet for TOCI, a number of other randomized-controlled trials provide supplemental data about the efficacy of TOCI as a treatment for COVID-19. Information about these trials is included in Table 2 below.

- The majority of the trials in table 2 excluded patients with another active bacterial, fungal or viral infection, those with an ANC < 1000/uL, platelet count < 50 cells/uL, AST or ALT > 5-10 x upper limit of normal. Immunosuppression and history of diverticulitis or bowel perforation were other common exclusion criteria.

Table 2: Other Randomized Trials of Tocilizumab for COVID-19

Study	Design/population	Outcomes	Demographics	Results
REMAP-CAP[11] Multiple countries	Open-label RCT of critically ill adults with COVID requiring respiratory or cardiovascular organ support within 24 hours of ICU admission. Multiple arms including TOCI (n=353), sarilumab (n=48), or standard care (n=402)	Number respiratory and cardiovascular support free days up to day 21	Mean age 61 yrs, 73% male, 72% white. 33% received remdesivir. 93% of those enrolled after RECOVERY received steroids. Majority were on NIV/MV	**Median number of organ support-free days: TOCI 10 vs. 0 with std care. In hospital mortality for pooled TOCI/sarilumab was 27% vs. 36% std care** *Note: this was a critically ill population treated very early in the ICU admission*
TOCIBRAS[12] Brazil	Open-label RCT: patients with severe COVID-19 (infiltrates and oxygen supplementation to maintain O_2 sat >93%) and lab evidence of hyperinflammation. TOCI (n=65) vs. std. care (n=64)	Clinical status at day 15 by ordinal scale, 28 day mortality, in-hospital mortality	Mean age 57 yrs, 68% male, most had comorbidities. Steroids in 69% TOCI and 73% std care patients. Most were on low-flow (60%/44% or high-flow O_2 (23%/41%)	**Trial was stopped early due to excess of deaths in the TOCI arm**. Mortality at day 15 was 17% vs. 3% *Note: more patients in the standard care arm were on high-flow O_2 or non-invasive ventilation at baseline*
BACC[13] Boston, USA	Double-blind, placebo-controlled RCT in hosp. patients with severe COVID-19 (infiltrates or O_2 supp. To maintain sat >92% but not > 10 L/min) and evidence hyperinflamm. TOCI (n=161) vs. placebo (n=81)	Need for MV or death by day 28	Median age 60 yrs, 30% received remdesivir but only 11% TOCI and 6% placebo received steroids. Majority were on low-flow O_2	**No difference in any outcom**e – need for MV or death in 11% vs. 13% *Note: this was a blinded RCT of relatively low severity patients not receiving steroids.*
CORIMUNO-TOCI- 1[14] France	Open-label RCT in hospitalized patients on O_2 but not NIV/MV. TOCI (n=64) vs. std care (n=67)	Need for NIV/MV by day 14 or survival without NIV/MV by day 14	Median age 64 yrs, majority male, more patients in the usual care group received steroids (61% vs. 33%) and antivirals (24% vs. 11%)	**No difference in outcomes,** *Note: this was a small trial of low-severity patients with some differences in the use of other therapies.*
RCT-TCZ-COVID[15] Italy	Open-label RCT in hospitalized patients with severe COVID (P/F 200-300) not on NIV/ MV and evidence of hyperinflammation (by fever and CRP). TOCI (n=60) vs. std care (n=63)	Clinical worsening within 14 days (defined as need for MV or death or P/F<150)	Median age 60 yrs. 61% male, duration of symptoms 8 days. Very fewpatients included in analysis received steroids.	**No difference in primary outcome** – 10% vs. 8%, mortality or proportion discharged by day 14 or day 30. *Note: this was also a small trial of low-severity patients, with almost no concomitant corticosteroid use.*
COVINTOC[16] India	Open-label RCT in adults with mod-severe (defined as respiratory rate of 15-30/minute with an O_2 sat of 90-94%) or severe (respiratory rate ≥ 30/min and O_2 sat < 90% on room air, ARDS or septic shock). TOCI 6 mg/kg (n=91) vs. std. care (n=88)	Progression from moderate to severe or severe COVID to death	Median age 55 yrs., 85% male. 91% received steroids. Moderate disease in 45% (TOCI) vs. 53% (Std) and severe in 55% and 47%	**No difference in primary outcome:** progression at day 14: 9% vs. 13% (NS). At day 28, progression in severe patients was 16% vs. 34% (p=0.04) but NS in those with moderate COVID-19. *Note: this was a relatively small trial of mixed severity patients with some difference in severity (less severe patients with TOCI)*

Efficacy Summary:

- TOCI showed efficacy in **some**, but not **all** RCTs when used as a treatment for severe COVID-19. Given the criteria for EUA – that the totality of evidence suggests the known and suspected benefits may outweigh the known and unknown risks, the FDA granted an EUA for patients with severe COVID-19 who are also receiving corticosteroids. It is unclear which patients are most likely to derive a benefit from TOCI given the heterogeneous nature of patients in the trials and differences in outcomes seen with addition of TOCI to usual standard care.
- The NIH Consensus guidelines commented on TOCI on 5/24/21, and recommend a single dose of TOCI in combination with dexamethasone in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19, including:[17]
    - Recently hospitalized patients (within the first 3 days of hospitalization) who have been admitted to the ICU within the 24 hours prior and who require invasive mechanical ventilation, non-invasive ventilation or high-flow nasal cannula oxygen (> 40% FiO_2) OR
    - Recently hospitalized patients not admitted to the ICU who have rapidly increasing oxygen needs and require non-invasive ventilation or high-flow nasal cannula oxygen as above and have significantly increased markers of inflammation (CRP ≥ 75 mg/L)
    - *For those on conventional oxygen the guidelines state that while the addition of tocilizumab to their standard treatment may provide a modest benefit, there are insufficient evidence to specify which patients may benefit from TOCI. Some NIH Panel members would add tocilizumab to a patient's dexamethasone treatment in cases where the patient has rapidly increasing oxygen needs and C-reactive protein (CRP) levels ≥75 mg/L but does not yet require oxygen through high-flow nasal canula (HFNC) or noninvasive ventilation*
    - *The guidelines also state there are insufficient data on which patients, if any, are likely to benefit from a second dose*
    - ***It is unclear whether there is a clinical benefit for tocilizumab in patients who received invasive mechanical ventilation more than 24 hours after ICU admission.***
    - ***The NIH Guidelines state that TOCI should be AVOIDED in patients who are significantly immunosuppressed, particularly those with recent or other biologic immunomodulating drugs, and in patients who have high ALT, high risk for gastrointestinal perforation or have an uncontrolled serious bacteria, fungal or non-SARS-CoV-2 viral infection. In addition, for areas where strongyloidiasis is endemic, the NIH suggest considering prophylactic ivermectin in patients who will be treated with TOCI and corticosteroids***
- The recommendations in the NIH consensus guidelines are largely consistent with the FDA EUA although their recommendation is largely focused on patients who are ill enough to require higher levels of oxygen support and who have rapidly progressing respiratory disease. Providers should consider all available evidence when considering the use of TOCI in COVID-19, particularly in patients on lower levels of oxygen
- Guidelines from the Infectious Diseases Society of America also suggest TOCI in patients with progressive severe (O_2 sat ≤ 94% on room air or need for oxygen supplementation) or critical (need for mechanical ventilation or ECMO) who have elevated markers of systemic inflammation (Conditional recommendation, low certainty of evidence).[18]
- Many patients were excluded from the clinical trials, most notably those with an active infection, those with AST/ALT elevated more than 5-10 times ULN, patients with ANC < 1000/uL and platelets < 50,000. Given warnings and precautions, these factors should be taken into account when considering whether to administer TOCI in patients with COVID-19.

Tocilizumab Safety when used for COVID-19

What safety issues need to be considered when administering TOCI for COVID-19?*

- Safety data used to support the FDA EUA included data from EMPACTA, COVACTA and REMDACTA, which included a total of 974 patients exposed to TOCI. RECOVERY did not have extensive data related to adverse events (AE) and was not included in the safety information for the EUA. Note that although extensive safety data is available for TOCI when used as a treatment of rheumatoid arthritis, giant cell arteritis and CRS related to CAR-T cells, it is difficult to extrapolate as treatment of COVID-19 is only 1-2 doses vs. chronic administration, and the patient population differs considerably from those (other than CRS patient which may be more similar).

Contraindications:

- Tocilizumab is contraindicated in patients with known hypersensitivity to TOCI.

Warnings and precautions

- **Serious infections:** serious and sometimes fatal infections have been noted with TOCI, with pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis most commonly reported. Patients with other suspected active infections were typically excluded from RCTs of TOCI in COVID-19.
    - **TOCI should not be administered if patients have any other concurrent active infection, including localized infection**. If a patient develops a new infection while on treatment with TOCI, they should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient with appropriate antimicrobial therapy initiated and close monitoring.
    - Risks and benefits of treatment should be considered prior to initiating TOCI in patients with chronic or recurrent infection, or who have a history of a serious opportunistic infections
- **Gastrointestinal perforation**
    - Gastrointestinal perforation has been reported with chronic use of TOCI, primarily as a complication of diverticulitis. TOCI should be used with caution in patients who may be at increased risk of gastrointestinal perforation and new abdominal symptoms should prompt evaluation for early identification of perforation.
- **Hepatotoxicity**
    - During randomized trials of TOCI, treatment was associated with an increased risk of transaminase elevations and serious cases of hepatic injury have been observed in patients on chronic TOCI. The decision to administer TOCI in COVID should weigh the risks and benefits.
    - **TOCI is not recommended in patients with ALT or AST greater than 10 times the upper limit of normal.**
    - AST and ALT should be monitored during treatment according to standard practice.
- **Active hepatic disease and hepatic impairment**
    - **TOCI is not recommended in patients with active hepatic disease or hepatic impairment.**
- **Laboratory monitoring**
    - In RCTs, patient receiving TOCI had higher rates of neutropenia, thrombocytopenia and elevations of AST and ALT. Patients with baseline neutropenia, thrombocytopenia and elevated transaminases were excluded from most clinical trials of TOCI for COVID-19.
    - **TOCI is not recommended in patients with an absolute neutrophil count (ANC) < 1000/mm^3, platelet count < 50,000/mm^3 or ALT or AST more than 10 times the upper limit of the normal range.**
    - Monitor ALT/AST, neutrophils and platelet counts according to standard practice.
- **Hypersensitivity reactions**
    - Hypersensitivity reactions, including anaphylaxis have been reported with TOCI and fatal anaphylactic outcomes have been reported. These events have occurred as early as the first dose of TOCI.
    - TOCI should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis. If anaphylaxis occurs, stop TOCI immediately and discontinue TOCI permanently.
- **Demyelinating disorders**
    - Multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in RA clinical studies in patients on TOCI.
    - Monitor patients for signs and symptoms potentially indicative of demyelinating disorders and exercise caution when considering TOCI for COVID-19 in patients with pre-existing or recent history of these disorders.
- **Live vaccines**
    - Safety of using TOCI and live vaccines concurrently has not been established, including data on secondary transmission of infection from live vaccine or effectiveness of vaccine in patients on TOCI.

➢ Adverse events

- Selected safety data from the 3 blinded RCTs included in the FDA EUA of adverse reactions are included in Table 3

Table 3: Adverse reactions occurring in at least 3% of patients in the TOCI arm and more common than placebo in blinded RCTs

Study	EMPACTA		COVACTA		REDACTA	
Study arm	**TOCI**	**PLACEBO**	**TOCI**	**PLACEBO**	**TOCI**	**PLACEBO**
Constipation	6%	3%	NR	NR	13%	12%
Anxiety	6%	3%	NR	NR	3%	2%
Headache	3%	2%	NR	NR	NR	NR
Urinary tract infection	NR	NR	8%	3%	NR	NR
Acute kidney injury	NR	NR	7%	5%	NR	NR
Hypertension	NR	NR	7%	2%	NR	NR
Diarrhea	NR	NR	6%	2%	NR	NR
Delirium	NR	NR	5%	2%	NR	NR
Insomnia	NR	NR	4%	3%	5%	3%
Thrombocytopenia	NR	NR	4%	1%	3%	1%
ALT increased	NR	NR	3%	1%	NR	NR
Deep vein thrombosis	NR	NR	3%	2%	NR	NR
Pneumonia	NR	NR	NR	NR	8%	5%
Septic shock	NR	NR	NR	NR	6%	5%
Hypokalemia	NR	NR	NR	NR	5%	3%
Nausea	NR	NR	NR	NR	4%	3%
Hypoglycemia	NR	NR	NR	NR	3%	1%
Pain	NR	NR	NR	NR	3%	1%

Safety data from supportive trials of TOCI in COVID-19

➢ Interpretation of adverse event data from additional trials is limited by the fact that many were small, most were open-label and differed in populations studied and severity of illness. The data included below is intended to provide additional information but should be considered in light of the study design.

- **REMAP-CAP:** Nine serious AEs were reported in the TOCI arm – one secondary bacterial infection, 5 bleeding events, two cardiac events and one deterioration in vision. Eleven events in the control arm included 4 bleeding events and 7 thromboses.
- **TOCIBRAS:** AEs were reported in 43% of those receiving TOCI and 34% of those in the standard care arm. Serious ADEs were seen in 16% and 11%, respectively. No detectable difference in specific AEs were noted.
- **BACC:** Hypersensitivity reactions were noted in 1.2% of TOCI and 2.4% of placebo patients. Infection ≥ grade 3 was noted in 8% of TOCI and 17% of placebo patients. The only AE that was significantly greater with TOCI was neutropenia, which occurred in 14% of TOCI and 1% of placebo patients. Elevated ALT was seen in 5% of each group.
- **CORIMUNO-TOCI-1:** AEs were reported in 44% and 54% of TOCI and usual care arms, respectively. Serious AEs occurred in 32% and 43%, respectively. There were 2 serious bacterial infections in the TOCI group vs. 11 in the usual care arm.
- **RCT-TCZ-COVID:** AEs were reported in 23% of subjects receiving TOCI vs. 11% in the standard care arm. The most

common AEs were increased ALT and decreased neutrophil count. Only 3 serious AEs occurred in this trial, 2 severe infections in the standard care group and one upper gastrointestinal bleeding event in the TOCI arm (none were considered treatment related).

- **COVINTOC:** AEs were seen in 36% and 25% of TOCI and standard care arms, respectively, with severe AEs in 20% and 17%. The most common serious AEs were ARDS, shock, cardiac disorders and multiple organ dysfunction.

Safety summary of TOCI in COVID-19

- The adverse event profile of TOCI has been well-described when used for chronic rheumatologic conditions and includes a risk of severe infections, including opportunistic infections, neutropenia, thrombocytopenia, elevation in hepatic transaminases, gastrointestinal perforation and hypersensitivity reactions.
- It is unclear whether rare adverse events above would be observed if larger numbers of patients from trials of COVID-19 were available but most of the existing RCTs do not show a significantly elevated risk of infection, although there were numerical imbalances in both directions.
- Considering patients at high risk for these adverse events were largely excluded from clinical trials, it is unclear if the risk of adverse events of special interest would be higher and the EUA recommends against use in some of these patient populations (e.g. active infection, elevation in transaminases more than 10 times upper limit of normal, platelets less than 50,000/mm^3, neutropenia)
- Providers are required to report all medication errors and serious adverse events through VA ADERS as a MedWatch report (see below) within 7 days. In particular, providers should review events that are known adverse events of TOCI when used for chronic rheumatologic disorders and consider whether they may be related to TOCI, and submitted as a VA ADERS report to support VA Surveillance activities.

Will the VA be monitoring for adverse events associated with TOCI for COVID-19?

- YES – VA has been monitoring the safety of Tocilizumab as an off-label use agent in Veteran inpatients with COVID-19 through VA ADERS and through real time surveillance [19] Given the limited safety data, vigilance in monitoring for adverse events is critical. Physicians, nurses, pharmacists and other healthcare providers should be monitoring patients closely for unusual clinical or laboratory events, record them as per local policy and report them to VA ADERS.
- All COVID-19 related ADEs are to be reported as per local policy and to VA ADERS as a MedWatch report (a separate FDA MedWatch report is not required when submitted in VA ADERS). ADEs are reported to VA ADERS using the following link: https://vaww.cmop.med.va.gov/MedSafe_Portal/
- VHA Center for Medication Safety will also be conducting prospective pharmacovigilance to identify potential adverse events and will report those to the FDA .

Other issues

What other things are important to know about TOCI or about the FDA EUA

- Information on the FDA Emergency Use Authorization can be found on the FDA website: FDA Emergency Use Authorization Letter for TOCI for COVID-19
  Important additional documents include the
  - Fact sheet for healthcare providers
  - Fact sheet for patients and caregivers

- **Instructions for Healthcare Providers:**
  - Healthcare providers must communicate to the patient or parent/caregiver/surrogate decision maker (SDM), as age appropriate, information consistent with the "Fact Sheet for Patients, Parents and Caregivers" (and provider a copy of the fact sheet) prior to the patient receiving tocilizumab, including:
    - FDA has authorized the emergency use of tocilizumab to treat COVID-19 in hospitalized patients who are receiving corticosteroids AND who require supplemental oxygen, invasive/non-invasive mechanical ventilation or ECMO.
    - The patient or parent/caregiver/SDM has the option to accept or refuse TOCI.
    - The significant known and potential risks and benefits of TOCI and the extent to which such potential benefits and risks are unknown.
    - Information on available alternative treatments and the risks and benefits of those alternatives, including clinical trials.
  - If providing this information will delay the administration of TOCI to a degree that would endanger the lives of

patients, the information must be provided to the patients as soon as practicable after TOCI is administered.

- Provider is responsible for reporting all medication errors and severe adverse events potentially related to treatment within 7 calendar days and respond to FDA request for information about adverse events.

➢ **Mandatory requirements for TOCI for COVID-19 under Emergency Use Authorization:**

- VA participation in the EUA program is contingent on the following information being reported to the FDA
  - Patient-specific information on those receiving TOCI for COVID-19 (patient name, age, disease manifestation, number of doses administered, other drugs administered)
  - That appropriate storage and cold-chain was maintained until the product is administered
  - Administration information including which lots were received, when they were received, product storage and what outcomes occurred
  - Adverse drug events must be documented in accordance with local policy and ALSO placed in the VA ADERS program.

How do I obtain TOCI for a patient with COVID-19 at my facility?

➢ Tociizumab can be obtained via prime vendor orders through normal ordering procedures. Please note that there will not be separate McKesson item numbers for product purchased to be used for COVID-19 under the EUA. In addition to local approval processes; to remain compliant with requirements from the FDA, facilities interested in treating patients with TOCI for COVID-19 **must** submit a patient-specific request on the PBM EUA portal**:**

- Facilities that are eligible to provide EUA products must initiate a request that provides:
  - Patient name, last four of SSN, date of birth, and date of positive COVID-19 test
  - Documentation that the patient meets all criteria listed above
- Requests that meet all specified criteria will be automatically approved. After approval is obtained, the site may initiate therapy.
- Upon completion of therapy, the site must provide additional follow-up information including:
  - Which lots were administered
  - When the package arrived
  - Total number of doses given to the patient
  - Date/time therapy initiated and completed
  - If and adverse drug events occurred, and if they were documented appropriately
  - Certification that all information above was completed wholly and accurately (sites may choose to begin adding follow-up information before therapy is completed, and the information will not be considered final until certified).
- ANY Adverse drug events that occur must be documented in accordance with local policy and ALSO placed in the VA ADERS program
- Refer to PBM EUA portal for additional help and any updates or changes.

➢ Healthcare facilities and healthcare providers must ensure that appropriate storage is maintained until the authorized product is administered consistent with the terms of this letter

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