FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR ACTEMRA® (tocilizumab)

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use ACTEMRA under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for ACTEMRA.

ACTEMRA® (tocilizumab) injection, for intravenous use
Original EUA Authorized Date: 06/2021

---------- EUA FOR ACTEMRA (tocilizumab)----------
The U.S. Food and Drug Administration (FDA) has issued an EUA for the emergency use of ACTEMRA 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 extracorporeal membrane oxygenation (ECMO). However, ACTEMRA is not FDA-approved for this use.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

----------DOSAGE AND ADMINISTRATION----------
The recommended dosage of ACTEMRA is a single 60-minute intravenous infusion as follows:

Patients less than 30 kg weight	12 mg/kg
Patients at or above 30 kg weight	8 mg/kg

If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of ACTEMRA may be administered at least 8 hours after the initial infusion.

Maximum dosage in COVID-19 patients is 800 mg per infusion.

Preparation and Administration
- For patients less than 30 kg, dilute to 50 mL in 0.9% or 0.45% Sodium Chloride Injection, USP for intravenous infusion using aseptic technique.
- For patients at or above 30 kg, dilute to 100 mL in 0.9% or 0.45% Sodium Chloride Injection, USP for intravenous infusion using aseptic technique.
- Administer as a single intravenous drip infusion over 1 hour; do not administer as bolus or push.

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to intravenous infusion (3)

----------CONTRAINDICATIONS----------
ACTEMRA is contraindicated in patients with known hypersensitivity to ACTEMRA (4)

----------WARNINGS AND PRECAUTIONS----------
- Serious Infections – do not administer ACTEMRA during any other concurrent active infection (5.1)
- Gastrointestinal (GI) perforation – use with caution in patients who may be at increased risk. (5.2)
- Hepatotoxicity – ACTEMRA treatment is not recommended in patients with elevated ALT or AST above 10 times the upper limit of the reference range. (5.3)
- Laboratory monitoring – recommended due to potential consequences of treatment-related changes in neutrophils, platelets, and liver function tests. (5.4)
- Hypersensitivity reactions, including anaphylaxis and death have occurred. (5.5)
- Live vaccines – avoid use with ACTEMRA. (5.8)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥ 3%) are constipation, anxiety, diarrhea, insomnia, hypertension and nausea (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to ACTEMRA (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Genentech at us_drug.safety@gene.com or call 1-888-835-2555 (6.2).

----------DRUG INTERACTIONS----------
Interactions with CYP450 Substrates: Caution should be exercised when co-administering ACTEMRA with CYP3A4 substrate drugs where decrease in effectiveness is undesirable. (7)

----------USE IN SPECIFIC POPULATIONS---
- Pregnancy: ACTEMRA should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. (8.1)
- Lactation: Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19. (8.2)
- Pediatric Use: ACTEMRA is not authorized or approved for emergency use for the treatment of coronavirus disease 2019 (COVID-19) in pediatric patients less than 2 years of age. (8.4)

See PATIENT AND PARENTS/CAREGIVER FACT SHEET.

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* Sections or subsections omitted from the EUA are not listed

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

1 EMERGENCY USE AUTHORIZATION

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. However, ACTEMRA is not FDA-approved for this use.

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

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, a novel coronavirus. The Secretary of Health and Human Services (HHS) has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.
- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is an FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition;
- The known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s); and
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Available Alternatives for the EUA Authorized Use

There is no adequate, approved and available alternative to ACTEMRA for treatment of adults and pediatric patients (2 years of age and older) hospitalized with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. For information on clinical studies of ACTEMRA and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for COVID-19

The recommended dosage for emergency use of ACTEMRA authorized under this EUA given as a single 60-minute intravenous infusion is:

Recommended Intravenous Dosage for COVID-19	
Patients less than 30 kg weight	12 mg/kg
Patients at or above 30 kg weight	8 mg/kg

If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of ACTEMRA may be administered at least 8 hours after the initial infusion.

Maximum Dosage in COVID-19 patients is 800 mg per infusion.

ACTEMRA subcutaneous administration is not authorized for the treatment of COVID-19 patients.

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

2.2 Preparation and Administration Instructions for Intravenous Infusion

ACTEMRA for intravenous infusion should be diluted by a healthcare professional using aseptic technique as follows:

- Use a sterile needle and syringe to prepare ACTEMRA.
- Patients **less than 30 kg**: use a **50 mL** infusion bag or bottle of 0.9% or 0.45% Sodium Chloride Injection, USP, and then follow steps 1 and 2 below.
- Patients **at or above 30 kg weight**: use a **100 mL** infusion bag or bottle of 0.9% or 0.45% Sodium Chloride Injection, USP, and then follow steps 1 and 2 below.

– Step 1. Withdraw a volume of 0.9% or 0.45% Sodium Chloride Injection, USP, equal to the volume of the ACTEMRA injection required for the patient's dose from the infusion bag or bottle (0.4 mL/kg and 0.6 mL/kg for 8 mg/kg and 12 mg/kg dosages, respectively)

– Step 2. Withdraw the amount of ACTEMRA 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.

  - The fully diluted ACTEMRA solutions for infusion using 0.9% Sodium Chloride Injection, USP may be stored at 36°F to 46°F (2°C to 8°C) or room temperature for up to 24 hours and should be protected from light.
  - The fully diluted ACTEMRA solutions for infusion using 0.45% Sodium Chloride Injection, USP may be stored at 36°F to 46°F (2°C to 8°C) for up to 24 hours or room temperature for up to 4 hours and should be protected from light.
  - ACTEMRA solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used.
  - Allow the fully diluted ACTEMRA solution to reach room temperature prior to infusion.
  - The infusion should be administered over 60 minutes, and must be administered with an infusion set. Do not administer as an intravenous push or bolus.

- ACTEMRA should not be infused concomitantly in the same intravenous line with other drugs. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of ACTEMRA with other drugs.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulates or discolorations are noted, the product should not be used.
- Fully diluted ACTEMRA solutions are compatible with polypropylene, polyethylene and polyvinyl chloride infusion bags and polypropylene, polyethylene and glass infusion bottles.

3 DOSAGE FORMS AND STRENGTHS

Injection: 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL as a clear, colorless to pale yellow solution in 20 mg/mL single-dose vials for further dilution prior to intravenous infusion.

4 CONTRAINDICATIONS

ACTEMRA is contraindicated in patients with known hypersensitivity to ACTEMRA.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

In COVID-19 patients, ACTEMRA should not be administered if patients have any other concurrent active infection, 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 most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Among opportunistic infections, tuberculosis, cryptococcus, aspergillosis, candidiasis, and pneumocystosis were reported with ACTEMRA. Other serious infections, not reported in clinical studies, may also occur (e.g., histoplasmosis, coccidioidomycosis, listeriosis).

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 with ACTEMRA, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants.

A patient who develops a new infection during treatment with ACTEMRA should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient; initiate appropriate antimicrobial therapy, and closely monitor the patient.

5.2 Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical trials for chronic indications, primarily as complications of diverticulitis, in patients treated with ACTEMRA. Use ACTEMRA 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.

5.3 Hepatotoxicity

Patients hospitalized with COVID-19 may have elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels. Multi-organ failure with involvement of the liver is recognized as a complication of severe COVID-19.

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 with ACTEMRA.

The decision to administer ACTEMRA should balance the potential benefit against the risks of acute treatment with ACTEMRA. 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.

5.4 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 *[see Warnings and Precautions (5.3)]*. Monitor ALT, AST, neutrophils and platelet counts according to current standard clinical practice.

5.5 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 of ACTEMRA. ACTEMRA for intravenous use should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis. If anaphylaxis or other hypersensitivity reaction occurs, stop administration of ACTEMRA immediately and discontinue ACTEMRA permanently. Do not administer ACTEMRA to patients with known hypersensitivity to ACTEMRA.

5.6 Demyelinating Disorders

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.

5.7 Active Hepatic Disease and Hepatic Impairment

ACTEMRA is not recommended in patients with active hepatic disease or hepatic impairment.

5.8 Vaccinations

Avoid use of live vaccines concurrently with ACTEMRA as clinical safety has not been established. The interval between live vaccinations and initiation of ACTEMRA therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ACTEMRA.

No data are available on the effectiveness of vaccination in patients receiving ACTEMRA.

Refer to Section 5 **Warnings and Precautions** of the FDA-approved Prescribing Information for additional safety information on risks associated with chronic use of ACTEMRA.

6 ADVERSE REACTIONS

The following clinically significant adverse reaction is described elsewhere in the Fact Sheet:

- Serious Infections *[see Warnings and Precautions (5.1)]*

6.1 Adverse Reactions from Clinical Studies

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.

The safety evaluation of ACTEMRA in COVID-19 was based on 4 clinical trials. These included one randomized, controlled, open-label, platform trial [Randomised Evaluation of COVID-19 Therapy (RECOVERY)] and 3 randomized, double-blind, placebo controlled trials (EMPACTA, COVACTA, and REMDACTA). Safety data from RECOVERY is not provided here as collection of adverse event data was limited. In EMPACTA, COVACTA, and REMDACTA, a total of 974 patients were exposed to ACTEMRA. Patients in EMPACTA, COVACTA, and REMDACTA received a single, 60-minute infusion of intravenous ACTEMRA 8 mg/kg (maximum dose of 800 mg). If clinical signs or symptoms worsened or did not improve, one additional dose of ACTEMRA 8 mg/kg could be administered between 8–24 hours after the initial dose.

<u>EMPACTA</u>

EMPACTA (NCT04372186) was a global, Phase 3, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of intravenous ACTEMRA in combination with standard of care (SoC) in hospitalized adult patients with COVID-19 pneumonia. The safety analysis was based on 250 patients in the ACTEMRA arm and 127 patients in the placebo arm.

During the study, there were 29 (12%) deaths in the ACTEMRA arm and 15 (12%) in the placebo arm. Serious adverse events occurred in 38 (15%) patients in the ACTEMRA arm and 25 (20%) in the placebo arm. Serious infections occurred in 13 (5%) patients in the ACTEMRA arm and 9 (7%) in the placebo arm. Adverse reactions occurring in at least 3% of patients in the ACTEMRA arm and more commonly than observed in the placebo arm are summarized in **Table 1**.

Table 1. Adverse Reactions Occuring in at Least 3% of Patients in the ACTEMRA Arm and More Commonly than Observed in the Placebo Arm Through Day 60[a]

Preferred Term	ACTEMRA N = 250 n (%)	PLACEBO N = 127 n (%)
Constipation	16 (6%)	4 (3%)
Anxiety	15 (6%)	4 (3%)
Headache	8 (3%)	3 (2%)

[a] Patients are counted once for each category regardless of the number of reactions

COVACTA

COVACTA (NCT04320615) was a global, Phase 3, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of intravenous ACTEMRA in combination with standard of care (SoC) in adult patients hospitalized with COVID-19 pneumonia. The safety analysis was based on 295 patients in the ACTEMRA arm and 143 patients in the placebo arm.

During the study, there were 72 (24%) deaths in the ACTEMRA arm and 36 (25%) in the placebo arm. Serious adverse events occurred in 116 (39%) patients in the ACTEMRA arm and 64 (45%) in the placebo arm. Serious infections occurred in 71 (24%) patients in the ACTEMRA arm and 42 (29%) in the placebo arm. Adverse reactions occurring in at least 3% of patients in the ACTEMRA arm and more commonly than observed in the placebo arm are summarized in **Table 2**.

Table 2. Adverse Reactions Occuring in at Least 3% of Patients in the ACTEMRA Arm and More Commonly than Observed in the Placebo Arm Through Day 60[a]

Preferred Term	ACTEMRA N = 295 n (%)	PLACEBO N = 143 n (%)
Urinary tract infection	24 (8%)	5 (3%)
Acute kidney injury	21 (7%)	7 (5%)
Hypertension	21 (7%)	3 (2%)
Diarrhea	18 (6%)	3 (2%)
Delirium	14 (5%)	3 (2%)
Insomnia	12 (4%)	5 (3%)
Thrombocytopenia	11 (4%)	2 (1%)
Alanine aminotransferase increased	10 (3%)	2 (1%)
Deep vein thrombosis	10 (3%)	3 (2%)

[a] Patients are counted once for each category regardless of the number of reactions

REMDACTA

REMDACTA (NCT04409262) was a global, Phase 3, randomized, double-blind, placebo-controlled, multicenter study conducted to assess the efficacy and safety of intravenous ACTEMRA in

combination with remdesivir (RDV) compared with matching placebo in combination with RDV in hospitalized patients with COVID-19 pneumonia; only adult patients enrolled. The safety analysis was based on 429 patients in the ACTEMRA + RDV arm and 213 patients in the placebo + RDV arm.

During the study, there were 98 (23%) deaths in the ACTEMRA + RDV arm and 55 (26%) deaths in the placebo +RDV arm. Serious adverse events occurred in 141 (33%) patients in the ACTEMRA + RDV arm and 76 (36%) in the placebo + RDV arm. Serious infections occurred in 97 (23%) patients in the ACTEMRA + RDV arm and 59 (28%) in the placebo + RDV arm. Adverse reactions occurring in at least 3% of patients in the ACTEMRA + RDV arm and more commonly than observed in the placebo + RDV arm are summarized in **Table 3**.

Table 3. Adverse Reactions Occuring in at Least 3% of Patients in the ACTEMRA + RDV Arm and More Commonly than Observed in the Placebo + RDV Arm Through Day 60[a]

Preferred Term	**ACTEMRA + RDV N = 429 n (%)**	**PLACEBO + RDV N = 213 n (%)**
Constipation	54 (13%)	25 (12%)
Pneumonia	33 (8%)	10 (5%)
Septic shock	24 (6%)	10 (5%)
Hypokalemia	23 (5%)	6 (3%)
Hyperglycemia	22 (5%)	9 (4%)
Insomnia	21 (5%)	7 (3%)
Nausea	19 (4%)	7 (3%)
Anxiety	14 (3%)	4 (2%)
Hypoglycemia	14 (3%)	2 (1%)
Thrombocytopenia	14 (3%)	2 (1%)
Pain	13 (3%)	2 (1%)

[a] Patients are counted once for each category regardless of the number of reactions
RDV=remdesivir

The most common adverse reactions (≥3%) reported in ACTEMRA-treated patients and at least 1% more commonly than in the placebo arm from the pooled safety-evaluable population from the Phase 3, randomized, double-blind, studies EMPACTA, COVACTA, and REMDACTA were constipation, anxiety, diarrhea, insomnia, hypertension, and nausea.

Refer to Section 6 **Adverse Reactions** of the FDA-approved Prescribing Information for additional information on adverse reactions associated with chronic use of ACTEMRA.

6.2 Required Reporting for Serious Adverse Events and Medication Errors

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, using FDA Form 3500 (for information on how to access this form, see below). The FDA recommends that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "ACTEMRA use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error"** heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #).

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

In addition, please 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.

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.

*Serious adverse events are defined as:

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

7 DRUG INTERACTIONS

7.1 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.

Refer to Section 7.2 **Drug Interactions** of the FDA-approved Prescribing Information for ACTEMRA for further details.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry
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.

Risk Summary
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.

Refer to Section 8.1 **Pregnancy** of the FDA-approved Prescribing Information for additional information on risks and data associated with chronic use of ACTEMRA.

8.2 Lactation

Risk Summary

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. Maternal immunoglobulin G (IgG) is present in human milk. If tocilizumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to tocilizumab are unknown. The lack of clinical data during lactation precludes clear determination of the risk of ACTEMRA to an infant during lactation; therefore the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ACTEMRA and the potential adverse effects on the breastfed child from tocilizumab or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

8.4 Pediatric Use

The FDA has granted an EUA for the emergency use of ACTEMRA for the treatment of 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. Pediatric use is supported by evidence justifying emergency use of ACTEMRA for the treatment of COVID-19 in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO, as well as safety and dosing information of ACTEMRA in pediatric patients for other uses. However, ACTEMRA is not approved for this use *[see Dosage and Administration (2), Clinical Studies (14)]*.

ACTEMRA is not authorized or approved for the emergency use for patients younger than 2 years of age.

8.5 Geriatric Use

In EMPACTA, COVACTA, and REMDACTA combined, 375/973 (39%) patients in the ACTEMRA arm and 170/482 (35%) in the placebo arm were 65 years of age or older. No overall differences in safety or effectiveness of ACTEMRA were observed between patients 65 years of age and older and those less than 65 years of age in these studies.

In RECOVERY, 691/2022 (34%) patients allocated to ACTEMRA and 739/2094 (35%) patients allocated to usual care alone were 70 years of age or older. No overall differences in effectiveness of ACTEMRA were observed between patients 70 years of age and older and those less than 70 years of age in this study.

11 DESCRIPTION

Tocilizumab is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass with a typical H_2L_2 polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. ACTEMRA has a molecular weight of approximately 148 kDa. The antibody is produced in mammalian (Chinese hamster ovary) cells.

ACTEMRA (tocilizumab) injection is a sterile, clear, colorless to pale yellow, preservative-free solution for further dilution prior to intravenous infusion with a pH of approximately 6.5. Each single-dose vial, formulated with a disodium phosphate dodecahydrate/sodium dihydrogen phosphate dihydrate buffered solution, is available at a concentration of 20 mg/mL containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of ACTEMRA. Each mL of solution contains polysorbate 80 (0.5 mg), sucrose (50 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tocilizumab 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.

12.2 Pharmacodynamics

Refer to Section 12.2 **Pharmacodynamics** of the FDA-approved Prescribing Information for additional information on pharmacodynamics data associated with chronic use of ACTEMRA.

12.3 Pharmacokinetics

The pharmacokinetics of tocilizumab in COVID-19 adult patients was estimated by a population pharmacokinetic analysis of a dataset composed of 380 adult patients treated with 8 mg/kg intravenously.
For one dose of 8 mg/kg intravenous tocilizumab, the estimated median (range) Cmax and Cday28 of tocilizumab were 151 (77.5-319) mcg/mL and 0.229 (0.00119-19.4) mcg/mL, respectively.
For two doses of 8 mg/kg intravenous tocilizumab separated by 8 hours, the estimated median (range) Cmax of tocilizumab was 290 (152-604) mcg/mL.

Distribution

In COVID-19 adult patients treated with one or two infusions of 8 mg/kg intravenously separated by 8 hours, the estimated central volume of distribution was 4.52 L, and the estimated peripheral volume of distribution was 4.23 L, resulting in a volume of distribution of 8.75 L.

Elimination

In COVID-19 adult patients, serum concentrations were below the limit of quantification after 35 days on average following one infusion of intravenous 8 mg/kg. The average linear clearance in the population pharmacokinetic analysis was estimated to be 17.6 mL per hour in patients with baseline ordinal scale category 3 (OS 3, patients requiring supplemental oxygen), 22.5 mL per hour in patients with baseline OS 4 (patients requiring high-flow oxygen or non-invasive ventilation), 29 mL per hour in patients with baseline OS 5 (patients requiring mechanical ventilation), and 35.4 mL per hour in patients with baseline OS 6 (patients requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support).

Specific Populations

In COVID-19 adult patients, exposure following body-weight-based intravenous dosing (8 mg/kg tocilizumab up to 100 kg body weight with a maximum dose of 800 mg tocilizumab) was dependent on body weight and disease severity. Within a specified OS category, compared to patients with a mean body weight of 80 kg, exposure was 20% lower in patients weighing less than 60 kg. Exposure in patients weighing more than 100 kg was in the same range as exposure in patients with a mean body weight of 80 kg. For an 80 kg patient, exposure decreases as disease severity increases; for each category increase on the OS, exposure decreases consistently by 13%.

Refer to Section 12.3 **Pharmacokinetics** of the FDA-approved Prescribing Information for additional information on pharmacokinetics associated with chronic use of ACTEMRA.

14 CLINICAL STUDIES

14.1 Clinical Trials in Hospitalized Patients with COVID-19

The clinical evaluation of ACTEMRA in hospitalized COVID-19 patients was based on 4 clinical trials. These included one randomized, controlled, open-label, platform trial [Randomised Evaluation of COVID-19 Therapy (RECOVERY)] and 3 randomized, double-blind, placebo-controlled trials (EMPACTA, COVACTA, and REMDACTA).

RECOVERY

RECOVERY (NCT04381936) was a large, randomized, controlled, open-label, multi-center platform study conducted in the United Kingdom to evaluate the efficacy and safety of potential treatments in hospitalized adult patients with severe COVID-19 pneumonia. All eligible patients received usual care and underwent an initial (main) randomization. Eligible patients for the trial had clinically suspected or laboratory-confirmed SARS-CoV-2 infection and no medical contraindications to any of the treatments. Patients with clinical evidence of progressive COVID-19 (defined as oxygen saturation <92% on room air or receiving oxygen therapy, and CRP ≥75 mg/L) qualified for a second randomization to receive either intravenous ACTEMRA or usual care alone.

Efficacy analyses were performed in the intent-to-treat (ITT) population comprising 4116 patients who were randomized, with 2022 patients in the ACTEMRA + usual care arm and 2094 patients in the usual care alone arm.The mean age of participants was 63.6 years (standard deviation [SD] 13.6 years). The majority of patients were male (67%) and White (76%). At baseline, 14% of patients required invasive mechanical ventilation, 41% of patients required non-invasive ventilation or high-flow oxygen, and 45% of patients required low flow oxygen; 82% of patients were reported to be receiving systemic corticosteroids.

The primary outcome was time to death through Day 28. The hazard ratio comparing the ACTEMRA + usual care arm to the usual care alone arm was 0.85 (95% CI: 0.76 to 0.94), a statistically significant result ($p = 0.0028$). The probabilities of dying by Day 28 were estimated to be 30.7% and 34.9% in the ACTEMRA and usual care arms, respectively. The risk difference was estimated to be -4.1% (95% CI: -7.0% to -1.3%), consistent with the primary analysis. The hazard ratio among the pre-specified subgroup of patients receiving systemic corticosteroids at baseline was 0.79 (95% CI: 0.70 to 0.89), and for the pre-specified subgroup not receiving systemic corticosteroids at baseline was 1.16 (95% CI: 0.91 to 1.48).

The median time to hospital discharge was 19 days in the ACTEMRA + usual care arm and >28 days in the usual care arm (hazard ratio [95% CI] = 1.22 [1.12 to 1.33]).

Among patients not requiring invasive mechanical ventilation at baseline, the proportion of patients who required mechanical ventilation or died by Day 28 was 35% (619/1754) in the ACTEMRA + usual care arm and 42% (754/1800) in the usual care alone arm (risk ratio [95% CI] = 0.84, [0.77 to 0.92]).

EMPACTA

EMPACTA (NCT04372186) was a global, Phase 3, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of intravenous ACTEMRA in combination with standard of care (SoC) in hospitalized, non-ventilated adult patients with COVID-19 pneumonia. Eligible patients were at least 18 years of age, had confirmed SARS-CoV-2 infection by a positive reverse-transcriptase polymerase chain reaction (RT-PCR) result, had pneumonia confirmed by radiography, and had SpO2 < 94% on ambient air. Patients were randomized at a 2:1 ratio to receive one infusion of either 8 mg/kg ACTEMRA, with a maximum dose of 800 mg, or placebo. If clinical signs or symptoms worsened or did not improve, one additional infusion of blinded treatment of ACTEMRA or placebo could be given, 8–24 hours after the initial infusion.

Of the 389 patients who were randomized, efficacy analyses were performed in the modified intent-to-treat (mITT) population comprised of patients who received any amount of study medication, grouped as randomized (249 in the ACTEMRA arm; 128 in the placebo arm). In the mITT population (n=377)

at randomization, median age was 57 years (range 20-95); 59.2% of patients were male, 56.0% were of Hispanic or Latino ethnicity, 52.8% were White, 20.4% were American Indian/Alaska Native, 15.1% were Black/African American and 1.6% were Asian. At baseline, 35 (9.3%) patients were not on supplemental oxygen, 242 (64.2%) patients required low flow oxygen and 100 (26.5%) patients required high-flow oxygen. The median time from symptom onset was 8.0 days. At baseline, across treatment arms, 72.7% patients reported systemic corticosteroids use and 47.7% received remdesivir.

The primary efficacy endpoint was the cumulative proportion of patients who required mechanical ventilation or died by Day 28 estimated by the Kaplan-Meier method. For patients who received ACTEMRA, there was an observed improvement in the time to progression to mechanical ventilation or death compared to patients who received placebo (log-rank p value = 0.0360; HR [95% CI] = 0.56 [0.33 to 0.97]). The cumulative proportion of patients who required mechanical ventilation or died by Day 28 was 12.0% (95% CI, 8.52% to 16.86%) in the ACTEMRA arm and 19.3% (95% CI, 13.34% to 27.36%) in the placebo arm.

The median time to hospital discharge or “ready for discharge” (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen) through Day 28 was 6.0 days in the ACTEMRA arm and 7.5 days in the placebo arm (HR [95% CI]=1.16 [0.91 to 1.48]).

Mortality at Day 28 was 10.4% in the ACTEMRA arm versus 8.6% in the placebo arm (weighted difference (ACTEMRA arm - placebo arm): 2.0% [95% CI, -5.2% to 7.8%]).

COVACTA

COVACTA (NCT04320615) was a global, Phase 3, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of intravenous ACTEMRA in combination with standard of care (SoC) in adult patients hospitalized with severe COVID-19 pneumonia. Eligible patients were at least 18 years of age, had confirmed SARS-CoV-2 infection by a positive RT-PCR result, had pneumonia confirmed by radiography, and had oxygen saturation of 93% or lower on ambient air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less. Patients were randomized at a 2:1 ratio to receive one infusion of either 8mg/kg ACTEMRA, with a maximum dose of 800 mg, or placebo. If clinical signs or symptoms worsened or did not improve, one additional infusion of blinded treatment of ACTEMRA or placebo could be given, 8–24 hours after the initial infusion.

Of the 452 patients who were randomized, efficacy analyses were performed in the modified intent-to-treat (mITT) population comprised of patients who received any amount of study medication, grouped as randomized (294 in the ACTEMRA arm; 144 in the placebo arm). For the overall mITT population (n=438) at randomization, median age was 62 years (range 22-96); 69.9% of patients were male, 32.2% were of Hispanic or Latino ethnicity, 57.5% were White, 15.1% were Black/African American and 8.7% were Asian. At baseline, 3.4% of patients were not on supplemental oxygen, 27.9% were on low flow oxygen, 30.4% were on non-invasive ventilation or high flow oxygen, and 38.4% were on invasive mechanical ventilation. The median time from symptom onset was 11.0 days. At baseline, across treatment arms, 22.4% patients reported systemic corticosteroids use and 5.7% received remdesivir.

The primary efficacy endpoint was clinical status on Day 28 assessed on a 7-category ordinal scale consisting of the following categories:

1. Discharged (or “ready for discharge” as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen);
2. Non–ICU hospital ward (or “ready for hospital ward”), not requiring supplemental oxygen;
3. Non–ICU hospital ward (or “ready for hospital ward”), requiring supplemental oxygen;
4. ICU or non–ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen;
5. ICU, requiring intubation and mechanical ventilation;
6. ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy);
7. Death

There were no statistically significant differences observed in the distributions of clinical status on the 7-category ordinal scale at Day 28 when comparing the ACTEMRA arm to the placebo arm.

The median time to hospital discharge or “ready for discharge” was 20 days in the ACTEMRA arm and 28 days in the placebo arm (HR=1.35 [95% CI, 1.02 to 1.79]).

Mortality at Day 28 was 19.7% in the ACTEMRA arm versus 19.4% in the placebo arm (weighted difference (ACTEMRA arm - placebo arm): 0.3% [95% CI, -7.6 to 8.2]).

REMDACTA

REMDACTA (NCT04409262) was a global, Phase 3, randomized, double-blind, placebo-controlled, multicenter study conducted to assess the efficacy and safety of intravenous ACTEMRA in combination with remdesivir (RDV) compared with matching placebo in combination with RDV in hospitalized patients with severe COVID-19 pneumonia. Eligible patients were at least 12 years of age with confirmed SARS-CoV-2 infection, including a positive polymerase chain reaction (PCR) and pneumonia confirmed by radiography, and required supplemental oxygen > 6 L/min to maintain SpO2 >93%. Patients were randomized at a 2:1 ratio to receive blinded treatment of either ACTEMRA + RDV or a matching placebo + RDV. Study treatment was given in combination with standard of care. Patients assigned to the ACTEMRA + RDV arm received one infusion of ACTEMRA 8 mg/kg, with a maximum dose of 800 mg, and patients assigned to the placebo + RDV arm received one infusion of placebo. For both arms, if clinical signs or symptoms worsened or did not improve one additional infusion of blinded treatment of ACTEMRA or placebo could be given, 8–24 hours after the initial infusion.

Of the 649 patients who were randomized, efficacy analyses were performed in the modified intent-to-treat (mITT) population comprised of all patients who received any amount of ACTEMRA/placebo, grouped as randomized (430 in the ACTEMRA + RDV arm; 210 in the placebo + RDV arm). For the overall mITT population (n=640) at randomization, median age was 60 years (range 20-93); 63.3% of patients were male, 51.6% were Hispanic or Latino ethnicity, 67.0% were White, 10.9% were Black/African American and 3.4% were Asian. At baseline, 6.6% were on low flow oxygen, 79.8% were on non-invasive ventilation or high flow oxygen, and 13.6% were on invasive mechanical ventilation. The median time from symptom onset was 8 days. At baseline, the majority of patients had received corticosteroids (84.2% across treatment arms).

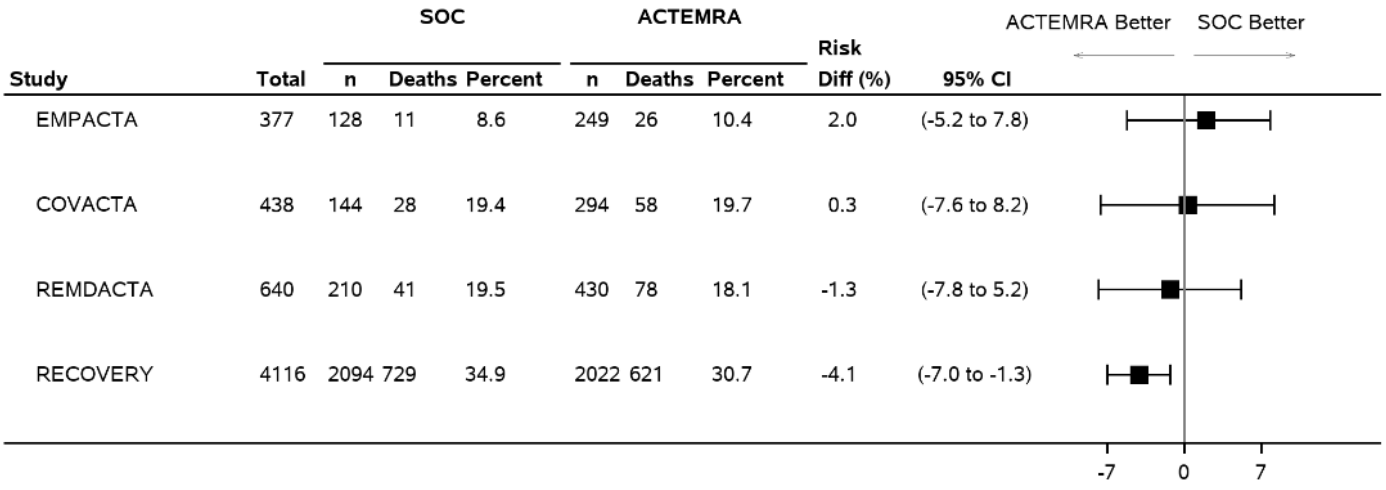
The primary efficacy endpoint was time from randomization to hospital discharge or “ready for discharge” up to Day 28. There were no statistically significant differences observed between treatment arms with respect to time to hospital discharge or “ready for discharge” through Day 28 (HR 0.965 [95% CI: 0.78 to 1.19]) or time to mechanical ventilation or death through Day 28 (HR 0.980 [95% CI: 0.72 to 1.34]).

Mortality at Day 28 was 18.1% in the ACTEMRA + RDV arm versus 19.5% in the placebo + RDV arm (weighted difference [ACTEMRA arm - placebo arm]: -1.3% [95% CI, -7.8% to 5.2%]).

Mortality Across Trials

Mortality outcomes were assessed at Day 28 across all 4 trials. These data, expressed as risk differences comparing ACTEMRA to placebo or standard of care treatment alone, are summarized in **Figure 1**.

Figure 1. Risk Differences Through Day 28 for EMPACTA, COVACTA, REMDACTA and RECOVERY



EMPACTA, COVACTA, and REMDACTA risk differences and 95% CIs were calculated as weighted differences using the Cochran-Mantel-Haenszel test stratified by study-specific stratification factors at randomization.
RECOVERY risk difference and 95% CI were estimated using the Kaplan-Meier approach.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ACTEMRA injection is a preservative-free, sterile clear, colorless to pale yellow solution. Under this EUA, ACTEMRA is supplied as 80 mg/4 mL (NDC 50242-135-01), 200 mg/10 mL (NDC 50242-136-01), and 400 mg/20 mL (NDC 50242-137-01) individually packaged 20 mg/mL single-dose vials for further dilution prior to intravenous infusion.

Storage and Handling

Do not use beyond expiration date on the container or package. ACTEMRA must be refrigerated at 36°F to 46°F (2ºC to 8ºC). Do not freeze. Protect the vials from light by storage in the original package until time of use.

17 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) and provide them with a copy of this Fact Sheet prior to administration of ACTEMRA. However, if providing this information will delay the administration of ACTEMRA 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.

18 MANUFACTURER INFORMATION

Manufactured by Genentech, Inc., A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990

To access the most recent ACTEMRA COVID-19 Fact Sheets and authorization letter, visit https://www.actemrahcp.com/covid-19.