ACTEMRA®
tocilizumab

Safety and Lab Monitoring Guide

With Subcutaneous or Intravenous Administration

INDICATION

ACTEMRA is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

IMPORTANT SAFETY INFORMATION

RISK OF SERIOUS INFECTIONS

Patients treated with ACTEMRA are at increased risk for developing serious infections that may lead to hospitalization or death, including tuberculosis (TB), bacterial, invasive fungal, viral, or other opportunistic infections. If a serious infection develops, interrupt ACTEMRA until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before ACTEMRA use and during therapy. Treatment for latent infection should be initiated prior to ACTEMRA use.**
- **Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with ACTEMRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ACTEMRA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

CONTRAINDICATION

ACTEMRA is contraindicated in patients with known hypersensitivity to ACTEMRA.

Please see accompanying full Prescribing Information and back cover for **Boxed WARNING** and additional Important Safety Information.

Monitoring Highlights: Key Warnings and Precautions[1]

For the management of adult patients with moderately to severely active RA and an inadequate response to DMARDs

Ongoing monitoring of your patient is important during the treatment of a chronic disease. Some biologic agents used in the treatment of RA have guidelines for the management of changes in laboratory values. ACTEMRA patients should be monitored for changes in lipids, hepatic transaminases, neutrophils, and platelets, as changes in these parameters were associated with treatment with ACTEMRA. Dosage modifications may be required.

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LIPIDS

4-8 WEEKS FOLLOWING INITIATION; THEN AT 6-MONTH INTERVALS (PI 5.3, 7.2)

WARNINGS: Treatment with ACTEMRA was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol.

LAB VALUE	
	SC IV Manage patients according to clinical guidelines (eg, National Cholesterol Educational Program [NCEP]) for the management of hyperlipidemia.
	SC IV Prescribers should exercise caution when ACTEMRA is coadministered with CYP3A4 substrate drugs where decrease in effectiveness is undesirable (eg, lovastatin, atorvastatin, simvastatin).

LIVER FUNCTION TESTS (ALT/AST)

4-8 WEEKS FOLLOWING INITIATION; THEN AT 3-MONTH INTERVALS (PI 2.9, 5.3)

WARNINGS: Treatment with ACTEMRA was associated with a higher incidence of transaminase elevations. These elevations did not result in apparent permanent or clinically evident hepatic injury in clinical trials. Increased frequency and magnitude of these elevations was observed when potentially hepatotoxic drugs (eg, methotrexate) were used in combination with ACTEMRA.

– It is not recommended to initiate ACTEMRA treatment in patients with elevated transaminases ALT or AST >1.5x upper limit of normal (ULN). In patients who develop elevated ALT or AST >5x ULN, treatment is not recommended.

LAB VALUE		
		SC IV Dose modify concomitant DMARDs dose, if appropriate.
>1 to 3x ULN		SC For persistent increases in this range: Reduce injection frequency to every other week or hold dosing until ALT or AST have normalized. Resume ACTEMRA 162 mg at every other week and increase frequency to every week as clinically appropriate. IV Reduce dose to 4 mg/kg or hold ACTEMRA until ALT or AST have normalized.
>3 to 5x ULN (confirmed by repeat testing)	SC IV	**Hold ACTEMRA Dosing** Until <3x ULN and follow recommendations above for >1 to 3x ULN. For persistent increases >3x ULN, discontinue ACTEMRA.
>5x ULN	SC IV	**Discontinue ACTEMRA**

NEUTROPHILS

4-8 WEEKS FOLLOWING INITIATION; THEN AT 3-MONTH INTERVALS (PI 2.9, 5.3, 12.2)

WARNINGS: Treatment with ACTEMRA was associated with a higher incidence of neutropenia. It is not recommended to initiate ACTEMRA treatment in patients with a low neutrophil count ie, absolute neutrophil count (ANC) less than 2000 per mm^3. In patients who develop an ANC less than 500 per mm^3, treatment is not recommended.

LAB VALUE (cells/mm^3)		
ANC >1000	SC IV	**Maintain ACTEMRA Dosing**
ANC ≥500 to ≤1000	SC IV	**Hold ACTEMRA Dosing** When ANC is greater than 1000 cells/mm^3: SC Resume ACTEMRA 162 mg at every other week and increase frequency to every week as clinically appropriate. IV Resume ACTEMRA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate.
ANC <500	SC IV	**Discontinue ACTEMRA**

PLATELETS

4-8 WEEKS FOLLOWING INITIATION; THEN AT 3-MONTH INTERVALS (PI 2.9, 5.3)

WARNINGS: Treatment with ACTEMRA was associated with a reduction in platelet counts. It is not recommended to initiate ACTEMRA in patients with a platelet count below 100,000 per mm^3. In patients who develop a platelet count less than 50,000 per mm^3, treatment is not recommended.

LAB VALUE (cells/mm^3)		
50,000 to 100,000	SC IV	**Hold ACTEMRA Dosing** When platelet count is greater than 100,000 cells/mm^3: SC Resume ACTEMRA 162 mg every other week and increase frequency to every week as clinically appropriate. IV Resume ACTEMRA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate.
<50,000	SC IV	**Discontinue ACTEMRA**

ALT=alanine transaminase; AST=aspartate transaminase; DMARD=disease-modifying antirheumatic drug; HDL=high-density lipoprotein; LDL=low-density lipoprotein; SC=subcutaneous.

ACTEMRA Dosing and Administration Guide for RA

Intravenous Infusion

DOSE	starting dose **4 mg/kg**	based on clinical response, increase dose to **8 mg/kg**
SCHEDULE	**EVERY 4 WEEKS**	

ACTEMRA IV Administration

ACTEMRA is administered as a 60-minute single intravenous drip infusion. Doses exceeding 800 mg per infusion are not recommended.

Reduction of dose from 8 mg/kg to 4 mg/kg is recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia.

Subcutaneous Administration

DOSE	**162 mg**		
SCHEDULE	for patients <100 kg/220 lb **ADMINISTER EVERY OTHER WEEK**	based on clinical response **INCREASE FREQUENCY TO EVERY WEEK**	for patients ≥100 kg/220 lb **ADMINISTER EVERY WEEK**

ACTEMRA SC Administration

Patients using ACTEMRA for subcutaneous administration should be instructed to inject the full amount in the syringe (0.9 mL), which provides 162 mg of ACTEMRA, according to the directions provided in the Instructions for Use.

Interruption of dose may be required for management of certain laboratory changes, including elevated liver enzymes, neutropenia, and thrombocytopenia.

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ACTEMRA® tocilizumab

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– It is not recommended to initiate ACTEMRA treatment in patients with elevated transaminases ALT or AST >1.5x upper limit of normal (ULN). In patients who develop elevated ALT or AST >5x ULN, treatment is not recommended.

LAB VALUE

>1 to 3x ULN	SC IV	Dose modify concomitant DMARDs dose, if appropriate.
	SC	For persistent increases in this range: Reduce injection frequency to every other week or hold dosing until ALT or AST have normalized. Resume ACTEMRA 162 mg at every other week and increase frequency to every week as clinically appropriate.
	IV	Reduce dose to 4 mg/kg or hold ACTEMRA until ALT or AST have normalized.
>3 to 5x ULN (confirmed by repeat testing)	SC IV	**Hold ACTEMRA Dosing** Until <3x ULN and follow recommendations above for >1 to 3x ULN. For persistent increases >3x ULN, discontinue ACTEMRA.
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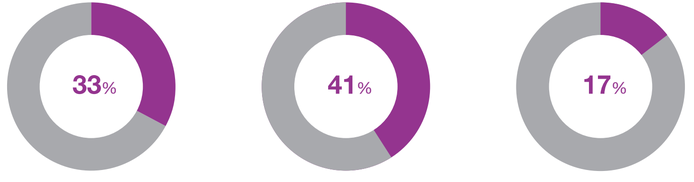
<50,000	SC IV	**Discontinue ACTEMRA**

ALT=alanine transaminase; AST=aspartate transaminase; DMARD=disease-modifying antirheumatic drug; HDL=high-density lipoprotein; LDL=low-density lipoprotein; SC=subcutaneous.

Patients Taking ACTEMRA May Experience Increased LDL, Which Can Be Managed According to Clinical Guidelines[1]

- Mean LDL increased by 13 mg/dL in the ACTEMRA 4 mg/kg + DMARD arm, 20 mg/dL in the ACTEMRA 8 mg/kg + DMARD arm, and 25 mg/dL in the ACTEMRA 8 mg/kg monotherapy arm[1]
- Mean HDL increased by 3 mg/dL in the ACTEMRA 4 mg/kg + DMARD arm, 5 mg/dL in the ACTEMRA 8 mg/kg + DMARD arm, and 4 mg/dL in the ACTEMRA 8 mg/kg monotherapy arm[1]

Shift in Mean LDL From Baseline to Last Observation by ATP III Category in the ACTEMRA IV All-Exposure Population (N=3728)[2*†]



33% of patients evaluated had increased LDL from their baseline values[2]

- **22% of patients remained below 160 mg/dL**
- **10% of patients remained below 130 mg/dL**

41% of patients evaluated had consistent LDL from their baseline values[2]

17% of patients evaluated had decreased LDL from their baseline values[2]

Of 4171 patients, 443 were receiving lipid-lowering agents at baseline[2‡]

- 8.3% of patients in the study had missing values
- A smaller percentage of patients receiving lipid-lowering agents at baseline had increased LDL (24%) compared to patients not on lipid-lowering agents at baseline (33%)
- Elevated lipids responded to lipid-lowering agents[1]

Routine Monitoring[1]

Assess lipid parameters approximately 4 to 8 weeks following initiation of ACTEMRA therapy, then at approximately 24-week intervals. Manage patients according to clinical guidelines for the management of hyperlipidemia. Exercise caution when coadministering ACTEMRA with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, eg, oral contraceptives, lovastatin, atorvastatin, etc. The effect of ACTEMRA on CYP450 enzyme activity may persist for several weeks after stopping therapy.

*Percentages were calculated based on total patient population; patients with missing values at baseline or last assessment are not displayed.

†Care should be exercised in interpreting open-label results due to the inability to minimize bias.

‡Of 4171 patients, the 443 who received lipid-lowering agents from baseline had the following baseline lipid levels (mg/dL): <100 = 189; 100 to <130 = 114; 130 to <160 = 58; ≥160 = 31; missing value = 51.[2]

LDL values are in mg/dL.

ATP III=Adult Treatment Panel III.

ACTEMRA IV All-Exposure Population: Summary of Patterns of Neutropenia in Patients With Grade 3 or 4 Neutropenia[§]

Patterns of Neutropenia in Patients With a Grade 3 or 4 Neutrophil Count in 24-Week Randomized Controlled Trials[1]

ACTEMRA IV All-Exposure Population (N=4171)

	4 MG/KG ACTEMRA + DMARD PATIENTS (%)	8 MG/KG ACTEMRA + DMARD PATIENTS (%)	PLACEBO + DMARD PATIENTS (%)
Neutrophil Count Reduction <1000/mm^3	1.8	3.4	0.1
Neutrophil Count Reduction <500/mm^3	0.4	0.3	0.1

It is not recommended to initiate ACTEMRA treatment in patients with a low neutrophil count, ie, ANC <2000/mm^3. In patients who develop an ANC <500/mm^3, treatment is not recommended. Monitor neutrophils 4 to 8 weeks after start of therapy and every 3 months thereafter.[1]

Most Patients Who Developed Grade 3 or 4 Neutropenia Had it at Only One Visit (n=250)[2]

NEUTROPENIA INCIDENCE	NUMBER OF PATIENTS (%)
On single visit	143 (57.2)
On 2 consecutive visits	37 (14.8)
Sustained (>2 consecutive visits)[ll]	22 (8.8)
On nonconsecutive visits	48 (19.2)

There Was No Clear Relationship Between Decreases in Neutrophils Below 1000 per mm^3 and the Occurrence of Serious Infections[1]

[§]Grade 3=severe adverse event; Grade 4=life-threatening or disabling adverse event according to the Common Terminology Criteria for Adverse Events.[3]

[ll]Category includes patients with neutrophils <1 x 10^9/L, which occurred on more than 1 nonconsecutive visit. Patients are summarized in their worst category (with highest number of nonconsecutive visits considered the worst).

REFERENCES: 1. ACTEMRA [package insert]. South San Francisco, CA: Genentech, Inc. **2.** Data on file. Summary of Clinical Safety: 6-Month Pooled Data. Genentech, Inc, South San Francisco, CA. **3.** National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE); v4.0. Bethesda, MD: National Cancer Institute 2009. NIH publication 09-5410. Updated version CTCAE v4.03 published June 14, 2010.

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INDICATION

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IMPORTANT SAFETY INFORMATION

RISK OF SERIOUS INFECTIONS

Patients treated with ACTEMRA are at increased risk for developing serious infections that may lead to hospitalization or death, including tuberculosis (TB), bacterial, invasive fungal, viral, or other opportunistic infections. If a serious infection develops, interrupt ACTEMRA until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before ACTEMRA use and during therapy. Treatment for latent infection should be initiated prior to ACTEMRA use.**
- **Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with ACTEMRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ACTEMRA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

CONTRAINDICATION

ACTEMRA is contraindicated in patients with known hypersensitivity to ACTEMRA.

WARNINGS AND PRECAUTIONS

***Gastrointestinal Perforations*:** Events of gastrointestinal (GI) perforation have been reported in clinical trials, primarily as complications of diverticulitis in RA patients. Use ACTEMRA with caution in patients who may be at increased risk for GI perforation. Promptly evaluate patients presenting with new-onset abdominal symptoms for early identification of GI perforation.

***Laboratory Parameters*:** Laboratory monitoring is recommended due to potential consequences of treatment-related laboratory abnormalities in neutrophils, platelets, lipids, and liver function tests. Dosage modifications may be required.

***Neutropenia*:** Treatment with ACTEMRA was associated with a higher incidence of neutropenia. It is not recommended to initiate ACTEMRA treatment in patients with a low neutrophil count i.e., absolute neutrophil count (ANC) less than 2000 per mm^3. In patients who develop an ANC less than 500 per mm^3 treatment is not recommended.

***Thrombocytopenia*:** Treatment with ACTEMRA was associated with a reduction in platelet counts. It is not recommended to initiate ACTEMRA in patients with a platelet count below 100,000 per mm^3. In patients who develop a platelet count less than 50,000 per mm^3, treatment is not recommended.

***Elevated Liver Enzymes*:** Treatment with ACTEMRA was associated with a higher incidence of transaminase elevations. These elevations did not result in apparent permanent or clinically evident hepatic injury in clinical trials. Increased frequency and magnitude of these elevations was observed when potentially hepatotoxic drugs (e.g., methotrexate) were used in combination with ACTEMRA.

– It is not recommended to initiate ACTEMRA treatment in patients with elevated transaminases ALT or AST >1.5x ULN. In patients who develop elevated ALT or AST >5x ULN, treatment is not recommended.

***Lipid Abnormalities*:** Treatment with ACTEMRA was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterols, and/or HDL cholesterol.

***Immunosuppression*:** The impact of treatment with ACTEMRA on the development of malignancies is not known, but malignancies were observed in clinical studies with ACTEMRA. ACTEMRA is an immunosuppressant, and treatment with immunosuppressants may result in an increased risk of malignancies.

***Hypersensitivity Reactions*:** 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. ACTEMRA for intravenous use should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis. For ACTEMRA subcutaneous injection, advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. 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.

Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials of intravenous ACTEMRA, 0.2% (8 out of 4009) of patients in the intravenous all-exposure RA population, 0.7% (8 out of 1068) in the subcutaneous 6-month controlled RA trials, and in 0.7% (10 out of 1465) of patients in the subcutaneous all-exposure population.

***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 clinical studies. Monitor patients for signs and symptoms of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent-onset demyelinating disorders.

***Active Hepatic Disease and Hepatic Impairment*:** Treatment with ACTEMRA is not recommended in patients with active hepatic disease or hepatic impairment.

***Vaccinations*:** Avoid use of live vaccines concurrently with ACTEMRA. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ACTEMRA or on the effectiveness of vaccination in patients receiving ACTEMRA. Patients should be brought up to date on all recommended vaccinations prior to initiation of ACTEMRA therapy.

ADVERSE REACTIONS

RHEUMATOID ARTHRITIS (RA)

The most common serious adverse reactions were serious infections. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. In the ACTEMRA-IV monotherapy clinical study, the rate of serious infections was 3.6 per 100 patient-years in the ACTEMRA group and 1.5 per 100 patient-years in the methotrexate group. The rate of serious infections in the 4 mg/kg and 8 mg/kg ACTEMRA plus DMARD groups was 4.4 and 5.3 events per 100 patient-years, respectively, compared to 3.9 events per 100 patient-years in the placebo plus DMARD group.

In the 5 Phase III clinical trials, the most common adverse reactions (≥5% of patients treated with ACTEMRA-IV) through 6 months were:

	ACTEMRA-IV 8 mg/kg Monotherapy (%)	Methotrexate (%)	ACTEMRA-IV 4 mg/kg + DMARDs (%)	ACTEMRA-IV 8 mg/kg + DMARDs (%)	Placebo + DMARDs (%)
URTI	7	5	6	8	6
Nasopharyngitis	7	6	4	6	4
Headache	7	2	6	5	3
Hypertension	6	2	4	4	3
Increased ALT	6	4	3	3	1

The safety observed for ACTEMRA administered subcutaneously was consistent with the known safety profile of intravenous ACTEMRA, with the exception of injection-site reactions, which were more common with ACTEMRA-SC compared with placebo-SC injections (IV-arm).

In the 6-month control period, in SC-I, the frequency of injection-site reactions was 10.1% (64/631) and 2.4% (15/631) for the weekly ACTEMRA-SC and placebo-SC (IV-arm) group, respectively. In SC-II, the frequency of injection-site reactions was 7.1% (31/437) and 4.1% (9/218) for the every other week ACTEMRA-SC and placebo-SC groups, respectively. These injection-site reactions were mild to moderate in severity. The majority resolved without any treatment and none necessitated drug discontinuation.

DRUG INTERACTIONS

Cytochrome P450s in the liver are down-regulated by infection and inflammation stimuli including cytokines such as IL-6. Inhibition of IL-6 signaling in RA patients treated with ACTEMRA may restore CYP450 activities to higher levels than those in the absence of ACTEMRA leading to increased metabolism of drugs that are CYP450 substrates.

Exercise caution when coadministering ACTEMRA with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc.

USE IN PREGNANCY

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ACTEMRA during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

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.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

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