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

**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 HDL cholesterol.
- **SC** Manage patients according to clinical guidelines (eg, National Cholesterol Educational Program [NCEP]) for the management of hyperlipidemia.
- **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)**

- **4-6 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 significant 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.
- II It is not recommended to initiate ACTEMRA treatment in patients with elevated transaminases ALT or AST >3x upper limit of normal (ULN). In patients who develop elevated ALT or AST >5x ULN, treatment is not recommended.

**NEUTROPHILS**

- **4-6 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 (absolute neutrophil count [ANC] less than 1000 per mm³). In patients who develop an ANC less than 500 per mm³, treatment is not recommended.

**PLATELETS**

- **4-6 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 mm³. In patients who develop a platelet count less than 50,000 per mm³, treatment is not recommended.

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.

Please see accompanying full Prescribing Information and back cover for Boxed WARNING and additional Important Safety Information.
For the management of adult patients with moderately to severely active RA and an inadequate response to DMARDs.

Ongoing monitoring of your patient’s important during the treatment of a chronic disease. Some biological agents used in the treatment of RA have guidelines for the management of changes in laboratory values. ACTEMRA should be considered as part of a comprehensive risk management plan that includes careful monitoring of laboratory results in the management of RA.

### PATIENTS TAKING ACTEMRA MAY EXPERIENCE INCREASED LDL, WHICH CAN BE MANAGED ACCORDING TO CLINICAL GUIDELINES

- **LDL**: Increased LDL may occur in patients treated with ACTEMRA. The most common serious adverse reactions were serious infections. The most common adverse reactions observed in clinical trials were:
  - Neutropenia
  - Thrombocytopenia

#### WARNINGS:

**Boxed WARNING**

- Increased neutrophil counts and increased HDL levels may occur in patients treated with ACTEMRA.

**INCREASED SERUM LIPID LEVELS:**

- 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

- **CYP3A4 inhibitors:** Cytochrome P450s in the liver are down-regulated by infection and inflammation stimuli. As a result, the metabolism of ACTEMRA is decreased, leading to increased serum lipid levels. See Table 1 for a list of CYP3A4 inhibitors.

**INCREASED SERUM LIPID LEVELS:**

- The monitoring of serum lipids should be performed during treatment with ACTEMRA. In the ACTEMRA 4 mg/kg + DMARD arm, 25% of patients had elevations of lipids (78/631) and 2.4% (15/631) for the weekly ACTEMRA-SC and placebo-SC (IV-arm) group, respectively. The most common serious adverse reaction was serious infections. The most common adverse reactions observed in clinical trials were:
  - Neutropenia
  - Thrombocytopenia

#### ROUTINE MONITORING

- Access to lipids parameters approximately 4 to 6 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 administering ACTEMRA with CYP3A4 substrate drugs whose decrease in effectiveness is unknown, e.g., oral contraceptives, laxatives, antidepressants. The effect of ACTEMRA on CYP3A4 enzymes may persist for several weeks after stopping therapy.

#### PATIENTS TAKING ACTEMRA MAY EXPERIENCE INCREASED LDL, WHICH CAN BE MANAGED ACCORDING TO CLINICAL GUIDELINES

- Mean LDL increased by 13 mg/dL in the ACTEMRA 8 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.

- Mean LDL increased by 21 mg/dL in the ACTEMRA 8 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.

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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 mm³. In patients who develop an ANC less than 500 per mm³ 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 mm³. In patients who develop a platelet count less than 50,000 per mm³ 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 >1.5 x ULN. In patients who develop elevated ALT or AST >5 x ULN, treatment is not recommended.

Lipid Abnormalities: Treatment with ACTEMRA was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, 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% (8 out of 2644) of patients in the 6-month controlled trials of intravenous ACTEMRA, 0.2% (8 out of 400) 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.

Demelinating Disorders: The impact of treatment with ACTEMRA on demelinating disorders is not known, but multiple sclerosis and chronic inflammatory demelinating polyneuropathy were reported rarely in clinical studies. Monitor patients for signs and symptoms of demelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent-onset demelinating 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:

<table>
<thead>
<tr>
<th>Reaction</th>
<th>ACTEMRA-IV  8 mg/kg Monotherapy (%)</th>
<th>Methotrexate (%)</th>
<th>ACTEMRA-IV  4 mg/kg + DMARDs (%)</th>
<th>ACTEMRA-IV  8 mg/kg + DMARDs (%)</th>
<th>Placebo + DMARDs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>URTI</td>
<td>7</td>
<td>5</td>
<td>6</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>2</td>
<td>6</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>6</td>
<td>4</td>
<td>3</td>
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<td>1</td>
</tr>
</tbody>
</table>

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% (19/461) 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 P450 inhibitors 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 decreases 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.

You may report side effects to the FDA at (800) FDA-1085 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 635-2555.

Please see accompanying full Prescribing Information, including Boxed WARNING, for additional important safety information.