CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125276/S049

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ACTEMRA safely and effectively. See full prescribing information for ACTEMRA.

ACTEMRA® (tocilizumab)
Injection, for intravenous infusion
Initial U.S. Approval: 2010

WARNING: RISK OF SERIOUS INFECTIONS
See full prescribing information for complete boxed warning.
- **Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving ACTEMRA. (5.1)**
- **If a serious infection develops, interrupt ACTEMRA until the infection is controlled. (5.1)**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting ACTEMRA. (5.1)**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.1)	10/2012
Dosage and Administration (2.1)	10/2012
Warnings and Precautions (5.5)	10/2012

---------- INDICATIONS AND USAGE----------
ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor indicated for treatment of:

Rheumatoid Arthritis (1.1)
- Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

Systemic Juvenile Idiopathic Arthritis (SJIA) (1.2)
- Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

----------DOSAGE AND ADMINISTRATION----------
ACTEMRA may be used alone or in combination with methotrexate, and in RA, other DMARDs.

Rheumatoid Arthritis (2.1)
When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response.

Systemic Juvenile Idiopathic Arthritis (2.2)

Recommended SJIA Dosage Every 2 Weeks	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg

General Dosing Information (2.3)
- It is recommended that ACTEMRA not be initiated in patients with an absolute neutrophil count (ANC) below 2000 per mm^3, platelet count below 100,000 per mm^3, or who have ALT or AST above 1.5 times the upper limit of normal (ULN). (2.1, 5.3)
- ACTEMRA doses exceeding 800 mg per infusion are not recommended in RA patients. (2.1, 12.3)

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

Dose Modifications (2.4)
- Recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia.

---------- DOSAGE FORMS AND STRENGTHS ----------

Single-use vials of ACTEMRA (20 mg per mL):
- 80 mg per 4 mL (3)
- 200 mg per 10 mL (3)
- 400 mg per 20 mL (3)

---------- CONTRAINDICATIONS ----------
- ACTEMRA should not be administered to patients with known hypersensitivity to ACTEMRA (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Serious Infections – do not administer ACTEMRA during an active infection, including localized infections. If a serious infection develops, interrupt ACTEMRA until the infection is controlled. (5.1)
- Gastrointestinal (GI) perforation – use with caution in patients who may be at increased risk. (5.2)
- Laboratory monitoring – recommended due to potential consequences of treatment-related changes in neutrophils, platelets, lipids, and liver function tests. (2.4, 5.3)
- Hypersensitivity reactions, including anaphylaxis and death have occurred (5.5)
- Live vaccines – should not be given with ACTEMRA. (5.8, 7.3)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence of at least 5%): upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- USE IN SPECIFIC POPULATIONS ----------
- **Pregnancy:** Based on animal data, may cause fetal harm. Pregnancy registry available. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 10/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS INFECTIONS

Patients treated with ACTEMRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

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 *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis (RA)

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

1.2 Systemic Juvenile Idiopathic Arthritis (SJIA)

ACTEMRA® (tocilizumab) is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Rheumatoid Arthritis

ACTEMRA may be used as monotherapy or concomitantly with methotrexate or other DMARDs. The recommended dose of ACTEMRA for adult patients given as a 60-minute single intravenous drip infusion is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response.

- Reduction of dose from 8 mg per kg to 4 mg per kg is recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.4), Warnings and Precautions (5.3), and Adverse Reactions (6.1)]*.
- Doses exceeding 800 mg per infusion are not recommended in RA patients *[see Clinical Pharmacology (12.3)]*.

2.2 Systemic Juvenile Idiopathic Arthritis

ACTEMRA may be used alone or in combination with methotrexate. The recommended dose of ACTEMRA for SJIA patients given once every 2 weeks as a 60-minute single intravenous drip infusion is:

Recommended SJIA Dosage Every 2 Weeks	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg

- A change in dose should not be made based solely on a single visit body weight measurement, as weight may fluctuate.
- Interruption of dosing may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.4)]*.

2.3 General Considerations for Administration

- ACTEMRA has not been studied and its use should be avoided in combination with biological DMARDs such as TNF antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators because of the possibility of increased immunosuppression and increased risk of infection.
- It is recommended that ACTEMRA not be initiated in patients with an absolute neutrophil count (ANC) below 2000 per mm^3, platelet count below 100,000 per mm^3, or who have ALT or AST above 1.5 times the upper limit of normal (ULN).

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

- Systemic Juvenile Idiopathic Arthritis Patients less than 30 kg: utilize a **50 mL** infusion bag or bottle, then follow steps 1 and 2 below.
- Adult Rheumatoid Arthritis and SJIA patients at or above 30 kg weight: utilize a **100 mL** infusion bag or bottle, then follow steps 1 and 2 below.
  - Step 1. Withdraw a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of the ACTEMRA solution required for the patient's dose from the infusion bag or bottle.
  - Step 2. Slowly add ACTEMRA for intravenous infusion from each vial into the infusion bag or bottle. To mix the solution, gently invert the bag to avoid foaming.

- The fully diluted ACTEMRA solutions for infusion may be stored at 2° to 8°C (36° to 46°F) or room temperature for up to 24 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 and 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.

2.4 Dosage Modifications

ACTEMRA treatment should be interrupted if a patient develops a serious infection until the infection is controlled.

Rheumatoid Arthritis

Liver Enzyme Abnormalities *[see Warnings and Precautions (5.3)]:*	
Lab Value	**Recommendation**
Greater than 1 to 3x ULN	Dose modify concomitant DMARDs if appropriate For persistent increases in this range, reduce ACTEMRA dose to 4 mg per kg or interrupt ACTEMRA until ALT or AST have normalized
Greater than 3 to 5x ULN (confirmed by repeat testing)	Interrupt ACTEMRA dosing until less than 3x ULN and follow recommendations above for greater than 1 to 3x ULN For persistent increases greater than 3x ULN, discontinue ACTEMRA
Greater than 5x ULN	Discontinue ACTEMRA

Low Absolute Neutrophil Count (ANC) *[see Warnings and Precautions (5.3)]:*	
Lab Value (cells per mm^3)	**Recommendation**
ANC greater than 1000	Maintain dose
ANC 500 to 1000	Interrupt ACTEMRA dosing When ANC greater than 1000 cells per mm^3 resume ACTEMRA at 4 mg per kg and increase to 8 mg per kg as clinically appropriate
ANC less than 500	Discontinue ACTEMRA

Low Platelet Count *[see Warnings and Precautions (5.3)]:*	
Lab Value (cells per mm^3)	**Recommendation**
50,000 to 100,000	Interrupt ACTEMRA dosing When platelet count is greater than 100,000 cells per mm^3 resume ACTEMRA at 4 mg per kg and increase to 8 mg per kg as clinically appropriate
Less than 50,000	Discontinue ACTEMRA

Systemic Juvenile Idiopathic Arthritis:

Dose reduction of ACTEMRA has not been studied in the SJIA population. Dose interruptions of ACTEMRA are recommended for liver enzyme abnormalities, low neutrophil counts, and low platelet counts in patients with SJIA at levels similar to what is outlined above for patients with RA. If appropriate, concomitant methotrexate and/or other medications should be dose modified or stopped and ACTEMRA dosing interrupted until the clinical situation has been evaluated. In SJIA the decision to discontinue ACTEMRA for a laboratory abnormality should be based upon the medical assessment of the individual patient.

3 DOSAGE FORMS AND STRENGTHS

Single-use vials of ACTEMRA (20 mg per mL):

- 80 mg per 4 mL
- 200 mg per 10 mL
- 400 mg per 20 mL

4 CONTRAINDICATIONS

ACTEMRA should not be administered to patients with known hypersensitivity to ACTEMRA *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

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 for rheumatoid arthritis. The most common serious infections included pneumonia, urinary tract

infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis *[see Adverse Reactions (6.1)]*. 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). Patients have presented with disseminated rather than localized disease, and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids which in addition to rheumatoid arthritis may predispose them to infections.

ACTEMRA should not be administered in patients with an active infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating ACTEMRA in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of serious or an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored 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 *[see Dosage and Administration (2.3), Adverse Reactions (6.1), and Patient Counseling Information (17)]*.

ACTEMRA should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with ACTEMRA should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

Tuberculosis

Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating ACTEMRA.

Anti-tuberculosis therapy should also be considered prior to initiation of ACTEMRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Patients should be closely monitored for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

It is recommended that patients be screened for latent tuberculosis infection prior to starting ACTEMRA. The incidence of tuberculosis in worldwide clinical development programs is 0.1%. Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before initiating ACTEMRA.

Viral Reactivation

Viral reactivation has been reported with immunosuppressive biologic therapies and cases of herpes zoster exacerbation were observed in clinical studies with ACTEMRA. No cases of Hepatitis B reactivation were observed in the trials; however patients who screened positive for hepatitis were excluded.

5.2 Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical trials, primarily as complications of diverticulitis in RA patients. ACTEMRA should be used with caution in patients who may be at increased risk for gastrointestinal perforation. Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation *[see Adverse Reactions (6.1)]*.

5.3 Laboratory Parameters

Rheumatoid Arthritis

Neutrophils

Treatment with ACTEMRA was associated with a higher incidence of neutropenia. Infections have been uncommonly reported in association with treatment-related neutropenia in long-term extension studies and postmarketing clinical experience.

- 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 absolute neutrophil count less than 500 per mm^3 treatment is not recommended.
- Neutrophils should be monitored every 4 to 8 weeks *[see Clinical Pharmacology (12.2)]*. For recommended modifications based on ANC results *see Dosage and Administration (2.4)*.

Platelets

Treatment with ACTEMRA was associated with a reduction in platelet counts. Treatment-related reduction in platelets was not associated with serious bleeding events in clinical trials *[see Adverse Reactions (6.1)]*.

- It is not recommended to initiate ACTEMRA treatment 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.
- Platelets should be monitored every 4 to 8 weeks. For recommended modifications based on platelet counts *see Dosage and Administration (2.4)*.

Liver Function Tests

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 *[see Adverse Reactions (6.1)]*. Increased frequency and magnitude of these elevations was observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with ACTEMRA.

In one case, a patient who had received ACTEMRA 8 mg per kg monotherapy without elevations in transaminases experienced elevation in AST to above 10x ULN and elevation in ALT to above 16x ULN when MTX was initiated in combination with ACTEMRA. Transaminases normalized when both treatments were held, but elevations recurred when MTX and ACTEMRA were restarted at lower doses. Elevations resolved when MTX and ACTEMRA were discontinued.

- It is not recommended to initiate ACTEMRA treatment in patients with elevated transaminases ALT or AST greater than 1.5x ULN. In patients who develop elevated ALT or AST greater than 5x ULN treatment is not recommended.
- ALT and AST levels should be monitored every 4 to 8 weeks. When clinically indicated, other liver function tests such as bilirubin should be considered. For recommended modifications based on transaminases *see Dosage and Administration (2.4)*.

Lipids

Treatment with ACTEMRA was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol *[see Adverse Reactions (6.1)]*.

- Assessment of lipid parameters should be performed approximately 4 to 8 weeks following initiation of ACTEMRA therapy, then at approximately 24 week intervals.
- Patients should be managed according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.

Systemic Juvenile Idiopathic Arthritis

A similar pattern of liver enzyme elevation, low neutrophil count, low platelet count and lipid elevations is noted with ACTEMRA treatment in the SJIA population. Neutrophils, Platelets, ALT and AST should be monitored at the time of the second infusion and thereafter every 2 to 4 weeks. Lipids should be monitored as above for RA *[see Dosage and Administration (2.3)]*.

5.4 Immunosuppression

The impact of treatment with ACTEMRA on the development of malignancies is not known but malignancies were observed in clinical studies *[see Adverse Reactions (6.1)]*. ACTEMRA is an immunosuppressant, and treatment with immunosuppressants may result in an increased risk of malignancies.

5.5 Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis and death, have been reported in association with infusion of ACTEMRA *[see Adverse Reactions (6.1)]*. 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, and in 0.2% (8 out of 4009) of patients in the all-exposure rheumatoid arthritis population; and in the SJIA controlled trial, 1 out of 112 patients (0.9%). In the postmarketing setting, events of clinically significant hypersensitivity and anaphylaxis, including events with a fatal outcome, have occurred in patients treated with a range of doses of ACTEMRA, with or without concomitant arthritis therapies. Events have occurred in patients who received premedication. Clinically significant hypersensitivity and anaphylaxis events have occurred both with and without previous hypersensitivity reactions and as early as the first infusion of ACTEMRA *[see Adverse Reactions (6.2)]*. ACTEMRA should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis. If anaphylaxis or other clinically significant hypersensitivity reaction occurs, administration of ACTEMRA should be stopped immediately and ACTEMRA should be permanently discontinued. Do not administer ACTEMRA to patients with known hypersensitivity to ACTEMRA *[see Contraindications (4) and Adverse Reactions (6)]*.

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 RA clinical studies. Patients should be closely monitored 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

Treatment with ACTEMRA is not recommended in patients with active hepatic disease or hepatic impairment *[see Adverse Reactions (6.1), Use in Specific Populations (8.6)]*.

5.8 Vaccinations

Live vaccines should not be given concurrently with ACTEMRA as clinical safety has not been established. 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. Because IL-6 inhibition may interfere with the normal immune response to new antigens, it is recommended that all patients, particularly systemic juvenile idiopathic arthritis patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ACTEMRA therapy. The interval between live vaccinations and initiation of ACTEMRA therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

6 ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

6.1 Clinical Trials Experience

Rheumatoid Arthritis

The ACTEMRA data in rheumatoid arthritis (RA) includes 5 double-blind, controlled, multicenter studies. In these studies, patients received doses of ACTEMRA 8 mg per kg monotherapy (288 patients), ACTEMRA 8 mg per kg in combination with DMARDs (including methotrexate) (1582 patients), or ACTEMRA 4 mg per kg in combination with methotrexate (774 patients).

The all exposure population includes all patients in registration studies who received at least one dose of ACTEMRA. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3309 for at least one year; 2954 received treatment for at least 2 years and 2189 for 3 years.

All patients in these studies had moderately to severely active rheumatoid arthritis. The study population had a mean age of 52 years, 82% were female and 74% were Caucasian.

The most common serious adverse reactions were serious infections *[see Warnings and Precautions (5.1)]*. The most commonly reported adverse reactions in controlled studies up to 24 weeks (occurring in at least 5% of patients treated with ACTEMRA monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

The proportion of patients who discontinued treatment due to any adverse reactions during the double-blind, placebo-controlled studies was 5% for patients taking ACTEMRA and 3% for placebo-treated patients. The most common adverse reactions that required discontinuation of ACTEMRA were increased hepatic transaminase values (per protocol requirement) and serious infections.

Overall Infections

In the 24 week, controlled clinical studies, the rate of infections in the ACTEMRA monotherapy group was 119 events per 100 patient-years and was similar in the methotrexate monotherapy group. The rate of infections in the 4 mg per kg and 8 mg per kg ACTEMRA plus DMARD group was 133 and 127 events per 100 patient-years, respectively, compared to 112 events per 100 patient-years in the placebo plus DMARD group. The most commonly reported infections (5% to 8% of patients) were upper respiratory tract infections and nasopharyngitis.

The overall rate of infections with ACTEMRA in the all exposure population remained consistent with rates in the controlled periods of the studies.

Serious Infections

In the 24 week, controlled clinical studies, the rate of serious infections in the ACTEMRA monotherapy group was 3.6 per 100 patient-years compared to 1.5 per 100 patient-years in the methotrexate group. The rate of serious infections in the 4 mg per kg and 8 mg per kg ACTEMRA plus DMARD group 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 all-exposure population, the overall rate of serious infections remained consistent with rates in the controlled periods of the studies. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported *[see Warnings and Precautions (5.1)]*.

Gastrointestinal Perforations

During the 24 week, controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient-years with ACTEMRA therapy.

In the all-exposure population, the overall rate of gastrointestinal perforation remained consistent with rates in the controlled periods of the studies. Reports of gastrointestinal perforation were primarily reported as

complications of diverticulitis including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids, or methotrexate *[see Warnings and Precautions (5.2)]*. The relative contribution of these concomitant medications versus ACTEMRA to the development of GI perforations is not known.

Infusion Reactions

In the 24 week, controlled clinical studies, adverse events associated with the infusion (occurring during or within 24 hours of the start of infusion) were reported in 8% and 7% of patients in the 4 mg per kg and 8 mg per kg ACTEMRA plus DMARD group, respectively, compared to 5% of patients in the placebo plus DMARD group. The most frequently reported event on the 4 mg per kg and 8 mg per kg dose during the infusion was hypertension (1% for both doses), while the most frequently reported event occurring within 24 hours of finishing an infusion were headache (1% for both doses) and skin reactions (1% for both doses), including rash, pruritus and urticaria. These events were not treatment limiting.

Anaphylaxis

Clinically significant hypersensitivity reactions, including anaphylaxis associated with ACTEMRA and requiring treatment discontinuation were reported in 0.1% (3 out of 2644) in the 24 week, controlled trials and in 0.2% (8 out of 4009) in the all-exposure population. These reactions were generally observed during the second to fourth infusion of ACTEMRA. Appropriate medical treatment should be available for immediate use in the event of a serious hypersensitivity reaction *[see Warnings and Precautions (5.5)]*.

Laboratory Tests

Neutrophils

In the 24 week, controlled clinical studies, decreases in neutrophil counts below 1000 per mm^3 occurred in 1.8% and 3.4% of patients in the 4 mg per kg and 8 mg per kg ACTEMRA plus DMARD group, respectively, compared to 0.1% of patients in the placebo plus DMARD group. Approximately half of the instances of ANC below 1000 per mm^3 occurred within 8 weeks of starting therapy. Decreases in neutrophil counts below 500 per mm^3 occurred in 0.4% and 0.3% of patients in the 4 mg per kg and 8 mg per kg ACTEMRA plus DMARD, respectively, compared to 0.1% of patients in the placebo plus DMARD group. There was no clear relationship between decreases in neutrophils below 1000 per mm^3 and the occurrence of serious infections.

In the all-exposure population, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 24 week controlled clinical studies *[see Warnings and Precautions (5.3)]*.

Platelets

In the 24 week, controlled clinical studies, decreases in platelet counts below 100,000 per mm^3 occurred in 1.3% and 1.7% of patients on 4 mg per kg and 8 mg per kg ACTEMRA plus DMARD, respectively, compared to 0.5% of patients on placebo plus DMARD, without associated bleeding events.

In the all-exposure population, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 24 week controlled clinical studies *[see Warnings and Precautions (5.3)]*.

Liver Function Tests

Liver enzyme abnormalities are summarized in **Table 1**. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of ACTEMRA, or reduction in ACTEMRA dose, resulted in decrease or normalization of liver enzymes *[see Dosage and Administration (2.4)]*. These elevations were not associated with clinically relevant increases in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic insufficiency *[see Warnings and Precautions (5.3)]*.

Table 1 Incidence of Liver Enzyme Abnormalities in the 24 Week Controlled Period of Studies I to V*

	ACTEMRA 8 mg per kg MONOTHERAPY N = 288 (%)	Methotrexate N = 284 (%)	ACTEMRA 4 mg per kg + DMARDs N = 774 (%)	ACTEMRA 8 mg per kg + DMARDs N = 1582 (%)	Placebo + DMARDs N = 1170 (%)
AST (U/L)					
> ULN to 3x ULN	22	26	34	41	17
> 3x ULN to 5x ULN	0.3	2	1	2	0.3
> 5x ULN	0.7	0.4	0.1	0.2	< 0.1
ALT (U/L)					
> ULN to 3x ULN	36	33	45	48	23
> 3x ULN to 5x ULN	1	4	5	5	1
> 5x ULN	0.7	1	1.3	1.5	0.3

ULN = Upper Limit of Normal
*For a description of these studies, see Section 14, Clinical Studies.

In the all-exposure population, the elevations in ALT and AST remained consistent with what was seen in the 24 week, controlled clinical trials

Lipids

Elevations in lipid parameters (total cholesterol, LDL, HDL, triglycerides) were first assessed at 6 weeks following initiation of ACTEMRA in the controlled 24 week clinical trials. Increases were observed at this time point and remained stable thereafter. Increases in triglycerides to levels above 500 mg per dL were rarely observed. Changes in other lipid parameters from baseline to week 24 were evaluated and are summarized below:

- Mean LDL increased by 13 mg per dL in the ACTEMRA 4 mg per kg+DMARD arm, 20 mg per dL in the ACTEMRA 8 mg per kg+DMARD, and 25 mg per dL in ACTEMRA 8 mg per kg monotherapy.
- Mean HDL increased by 3 mg per dL in the ACTEMRA 4 mg per kg+DMARD arm, 5 mg per dL in the ACTEMRA 8 mg per kg+DMARD, and 4 mg per dL in ACTEMRA 8 mg per kg monotherapy.
- Mean LDL/HDL ratio increased by an average of 0.14 in the ACTEMRA 4 mg per kg+DMARD arm, 0.15 in the ACTEMRA 8 mg per kg+DMARD, and 0.26 in ACTEMRA 8 mg per kg monotherapy.
- ApoB/ApoA1 ratios were essentially unchanged in ACTEMRA-treated patients.

Elevated lipids responded to lipid lowering agents.

In the all-exposure population, the elevations in lipid parameters remained consistent with what was seen in the 24 week, controlled clinical trials.

Immunogenicity

In the 24 week, controlled clinical studies, a total of 2876 patients have been tested for anti-tocilizumab antibodies. Forty-six patients (2%) developed positive anti-tocilizumab antibodies, of whom 5 had an associated, medically significant, hypersensitivity reaction leading to withdrawal. Thirty patients (1%) developed neutralizing antibodies.

The data reflect the percentage of patients whose test results were positive for antibodies to tocilizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to tocilizumab with the incidence of antibodies to other products may be misleading.

Malignancies

During the 24 week, controlled period of the studies, 15 malignancies were diagnosed in patients receiving ACTEMRA, compared to 8 malignancies in patients in the control groups. Exposure-adjusted incidence was similar in the ACTEMRA groups (1.32 events per 100 patient-years) and in the placebo plus DMARD group (1.37 events per 100 patient-years).

In the all-exposure population, the rate of malignancies remained consistent with the rate observed in the 24 week, controlled period *[see Warnings and Precautions (5.4)]*.

Other Adverse Reactions

Adverse reactions occurring in 2% or more of patients on 4 or 8 mg per kg ACTEMRA plus DMARD and at least 1% greater than that observed in patients on placebo plus DMARD are summarized in **Table 2.**

Table 2 Adverse Reactions Occurring in at Least 2% or More of Patients on 4 or 8 mg per kg ACTEMRA plus DMARD and at Least 1% Greater Than That Observed in Patients on Placebo plus DMARD

24 Week Phase 3 Controlled Study Population					
Preferred Term	**ACTEMRA 8 mg per kg MONOTHERAPY N = 288 (%)**	**Methotrexate N = 284 (%)**	**ACTEMRA 4 mg per kg + DMARDs N = 774 (%)**	**ACTEMRA 8 mg per kg + DMARDs N = 1582 (%)**	**Placebo + DMARDs N = 1170 (%)**
Upper Respiratory Tract Infection	7	5	6	8	6
Nasopharyngitis	7	6	4	6	4
Headache	7	2	6	5	3
Hypertension	6	2	4	4	3
ALT increased	6	4	3	3	1
Dizziness	3	1	2	3	2
Bronchitis	3	2	4	3	3
Rash	2	1	4	3	1
Mouth Ulceration	2	2	1	2	1
Abdominal Pain Upper	2	2	3	3	2
Gastritis	1	2	1	2	1
Transaminase increased	1	5	2	2	1

Other infrequent and medically relevant adverse reactions occurring at an incidence less than 2% in rheumatoid arthritis patients treated with ACTEMRA in controlled trials were:

Infections and Infestations: oral herpes simplex
Gastrointestinal disorders: stomatitis, gastric ulcer
Investigations: weight increased, total bilirubin increased
Blood and lymphatic system disorders: leukopenia
General disorders and administration site conditions: edema peripheral
Respiratory, thoracic, and mediastinal disorders: dyspnea, cough
Eye disorders: conjunctivitis
Renal disorders: nephrolithiasis
Endocrine disorders: hypothyroidism

Systemic Juvenile Idiopathic Arthritis

The data described below reflect exposure to ACTEMRA in one randomized, double-blind, placebo-controlled trial of 112 pediatric patients with SJIA 2 to 17 years of age who had an inadequate clinical response to nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids due to toxicity or lack of efficacy. At baseline, approximately half of the patients were taking 0.3 mg/kg/day corticosteroids or more, and almost 70% were taking methotrexate. The trial included a 12 week controlled phase followed by an open-label extension.

In the 12 week double-blind, controlled portion of the clinical study 75 patients received treatment with ACTEMRA (8 or 12 mg per kg based upon body weight). After 12 weeks or at the time of escape, due to disease worsening, patients were treated with ACTEMRA in the open-label extension phase.

The most common adverse events (at least 5%) seen in ACTEMRA treated patients in the 12 week controlled portion of the study were: upper respiratory tract infection, headache, nasopharyngitis and diarrhea.

Infections

In the 12 week controlled phase, the rate of all infections in the ACTEMRA group was 345 per 100 patient-years and 287 per 100 patient-years in the placebo group. In the open label extension over an average duration of 73 weeks of treatment, the overall rate of infections was 304 per 100 patient-years.

In the 12 week controlled phase, the rate of serious infections in the ACTEMRA group was 11.5 per 100 patient years. In the open label extension over an average duration of 73 weeks of treatment, the overall rate of serious infections was 11.4 per 100 patient years. The most commonly reported serious infections included pneumonia, gastroenteritis, varicella, and otitis media.

Macrophage Activation Syndrome

In the 12 week controlled study, no patient in any treatment group experienced macrophage activation syndrome (MAS) while on assigned treatment; 3 per 112 (3%) developed MAS during open-label treatment with ACTEMRA. One patient in the placebo group escaped to ACTEMRA 12 mg per kg at Week 2 due to severe disease activity, and ultimately developed MAS at Day 70. Two additional patients developed MAS during the long-term extension. All 3 patients had ACTEMRA dose interrupted (2 patients) or discontinued (1 patient) for the MAS event, received treatment, and the MAS resolved without sequelae. Based on a limited number of cases, the incidence of MAS does not appear to be elevated in the ACTEMRA SJIA clinical development experience; however no definitive conclusions can be made.

Infusion Reactions

Patients were not premedicated, however most patients were on concomitant corticosteroids as part of their background treatment for SJIA. Infusion related reactions were defined as all events occurring during or within 24 hours after an infusion. In the 12 week controlled phase, 4% of ACTEMRA and 0% of placebo treated patients experienced events occurring during infusion. One event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment.

Within 24 hours after infusion, 16% of patients in the ACTEMRA treatment group and 5% of patients in the placebo group experienced an event. In the ACTEMRA group the events included rash, urticaria, diarrhea, epigastric discomfort, arthralgia and headache. One of these events, urticaria, was considered serious.

Anaphylaxis

Anaphylaxis was reported in 1 out of 112 patients (less than 1%) treated with ACTEMRA during the controlled and open label extension study *[see Warnings (5.5)]*.

Immunogenicity

All 112 patients were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti-tocilizumab antibodies: one of these patients experienced serious adverse events of urticaria and angioedema consistent with an anaphylactic reaction which led to withdrawal; the other patient developed macrophage activation syndrome while on escape therapy and was discontinued from the study.

Laboratory Tests

Neutrophils

During routine monitoring in the 12 week controlled phase, a decrease in neutrophil below 1×10^9 per L occurred in 7% of patients in the ACTEMRA group, and in no patients in the placebo group. In the open label extension over an average duration of 73 weeks of treatment, a decreased neutrophil count occurred in 17% of

the ACTEMRA group. There was no clear relationship between decrease in neutrophils below 1 x 10^9 per L and the occurrence of serious infections.

Platelets

During routine monitoring in the 12 week controlled phase, 1% of patients in the ACTEMRA group and 3% in the placebo group had a decrease in platelet count to no more than 100 × 10^3 per mcL.

In the open label extension over an average duration of 73 weeks of treatment, decreased platelet count occurred in 4% of patients in the ACTEMRA group, with no associated bleeding.

Liver Function Tests

During routine laboratory monitoring in the 12 week controlled phase, elevation in ALT or AST at or above 3x ULN occurred in 5% and 3% of patients, respectively in the ACTEMRA group and in 0% of placebo patients.

In the open label extension over an average duration of 73 weeks of treatment, the elevation in ALT or AST at or above 3x ULN occurred in 13% and 5% of ACTEMRA treated patients, respectively.

Lipids

During routine laboratory monitoring in the 12 week controlled phase, elevation in total cholesterol greater than 1.5x ULN – 2x ULN occurred in 1.5% of the ACTEMRA group and in 0% of placebo patients. Elevation in LDL greater than 1.5x ULN – 2x ULN occurred in 1.9% of patients in the ACTEMRA group and 0% of the placebo group.

In the open label extension study over an average duration of 73 weeks of treatment, the pattern and incidence of elevations in lipid parameters remained consistent with the 12 week controlled study data.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ACTEMRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Fatal anaphylaxis *[see Warnings and Precautions (5.5)]*

7 DRUG INTERACTIONS

7.1 Other Drugs for Treatment of Rheumatoid Arthritis

Population pharmacokinetic analyses did not detect any effect of methotrexate (MTX), non-steroidal anti-inflammatory drugs or corticosteroids on tocilizumab clearance.

Concomitant administration of a single dose of 10 mg per kg ACTEMRA with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure.

ACTEMRA has not been studied in combination with biological DMARDs such as TNF antagonists *[see Dosage and Administration (2.1)]*.

7.2 Interactions with CYP450 Substrates

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 tocilizumab may restore CYP450 activities to higher levels than those in the absence of tocilizumab leading to increased metabolism of drugs that are CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Its effects on CYP2C8 or transporters is unknown. In vivo studies with omeprazole, metabolized by CYP2C19 and CYP3A4, and simvastatin, metabolized by CYP3A4, showed up to a 28% and 57% decrease in exposure one week following a single dose of ACTEMRA, respectively. The effect of tocilizumab on CYP enzymes may be

clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of ACTEMRA, in patients being treated with these types of medicinal products, therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) should be performed and the individual dose of the medicinal product adjusted as needed. Prescribers should exercise caution when ACTEMRA is coadministered with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc. The effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy *[see Clinical Pharmacology (12.3)]*.

7.3 Live Vaccines

Live vaccines should not be given concurrently with ACTEMRA *[see Warnings and Precautions (5.8)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. ACTEMRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

An embryo-fetal developmental toxicity study was performed in which pregnant cynomolgus monkeys were treated intravenously with tocilizumab (daily doses of 2, 10, or 50 mg per kg from gestation day 20-50) during organogenesis. Although there was no evidence for a teratogenic/dysmorphogenic effect at any dose, tocilizumab produced an increase in the incidence of abortion/embryo-fetal death at 10 mg per kg and 50 mg per kg doses (1.25 and 6.25 times the human dose of 8 mg per kg every 2 to 4 weeks based on a mg per kg comparison).

Nonteratogenic Effects. Testing of a murine analogue of tocilizumab in mice did not yield any evidence of harm to offspring during the pre- and postnatal development phase when dosed at 50 mg per kg intravenously with treatment every three days from implantation until day 21 after delivery (weaning). There was no evidence for any functional impairment of the development and behavior, learning ability, immune competence and fertility of the offspring.

Pregnancy Registry: To monitor the outcomes of pregnant women exposed to ACTEMRA, a pregnancy registry has been established. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

8.3 Nursing Mothers

It is not known whether tocilizumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ACTEMRA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of ACTEMRA in pediatric patients with conditions other than SJIA have not been established. Children under the age of two have not been studied. Testing of a murine analogue of tocilizumab did not exert toxicity in juvenile mice. In particular, there was no impairment of skeletal growth, immune function and sexual maturation.

8.5 Geriatric Use

Of the 2644 patients who received ACTEMRA in Studies I to V *[see Clinical Studies (14)]*, a total of 435 rheumatoid arthritis patients were 65 years of age and older, including 50 patients 75 years and older. The frequency of serious infection among ACTEMRA treated subjects 65 years of age and older was higher than those under the age of 65. As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

8.6 Hepatic Impairment

The safety and efficacy of ACTEMRA have not been studied in patients with hepatic impairment, including patients with positive HBV and HCV serology *[see Warnings and Precautions (5.7)]*.

8.7 Renal Impairment

No dose adjustment is required in patients with mild renal impairment. ACTEMRA has not been studied in patients with moderate to severe renal impairment *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

No studies on the potential for ACTEMRA to cause dependence have been performed. However, there is no evidence from the available data that ACTEMRA treatment results in dependence.

10 OVERDOSAGE

There are limited data available on overdoses with ACTEMRA. One case of accidental overdose was reported in which a patient with multiple myeloma received a dose of 40 mg per kg. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received single doses of up to 28 mg per kg, although all 5 patients at the highest dose of 28 mg per kg developed dose-limiting neutropenia.

In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate symptomatic treatment.

11 DESCRIPTION

ACTEMRA (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.

ACTEMRA is supplied as a sterile, preservative-free solution for intravenous (IV) infusion at a concentration of 20 mg per mL. ACTEMRA is a colorless to pale yellow liquid, with a pH of about 6.5. Single-use vials are available containing 80 mg per 4 mL, 200 mg per 10 mL, or 400 mg per 20 mL of ACTEMRA. Injectable solutions of ACTEMRA are formulated in an aqueous solution containing disodium phosphate dodecahydrate and sodium dihydrogen phosphate dehydrate (as a 15 mmol per L phosphate buffer), polysorbate 80 (0.5 mg per mL), and sucrose (50 mg per mL).

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. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis.

12.2 Pharmacodynamics

In clinical studies with the 4 mg per kg and 8 mg per kg doses of ACTEMRA, decreases in levels of C-reactive protein (CRP) to within normal ranges were seen as early as week 2. Changes in pharmacodynamic parameters were observed (i.e., decreases in rheumatoid factor, erythrocyte sedimentation rate (ESR), serum amyloid A and increases in hemoglobin) with both doses, however the greatest improvements were observed with 8 mg per kg

ACTEMRA. Pharmacodynamic changes were also observed to occur after ACTEMRA administration in SJIA patients (decreases in CRP, ESR, and increases in hemoglobin). The relationship between these pharmacodynamic findings and clinical efficacy is not known.

In healthy subjects administered ACTEMRA in doses from 2 to 28 mg per kg, absolute neutrophil counts decreased to the nadir 3 to 5 days following ACTEMRA administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. Rheumatoid arthritis patients demonstrated a similar pattern of absolute neutrophil counts following ACTEMRA administration *[see Warnings and Precautions (5.3)]*.

12.3 Pharmacokinetics

Rheumatoid Arthritis

The pharmacokinetics characterized in healthy subjects and RA patients suggested that PK is similar between the two populations. The clearance (CL) of tocilizumab decreased with increased doses. At the 10 mg per kg single dose in RA patients, mean CL was 0.29 ± 0.10 mL per hr per kg and mean apparent terminal $t_{1/2}$ was 151 ± 59 hours (6.3 days).

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis of 1793 rheumatoid arthritis patients treated with ACTEMRA 4 and 8 mg per kg every 4 weeks for 24 weeks.

The pharmacokinetic parameters of tocilizumab did not change with time. A more than dose-proportional increase in area under the curve (AUC) and trough concentration (C_{min}) was observed for doses of 4 and 8 mg per kg every 4 weeks. Maximum concentration (C_{max}) increased dose-proportionally. At steady-state, predicted AUC and C_{min} were 2.7 and 6.5-fold higher at 8 mg per kg as compared to 4 mg per kg, respectively. In a long-term study with dosing for 104 weeks, observed C_{min} was sustained over time.

For doses of ACTEMRA 4 mg per kg given every 4 weeks, the predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 13000 ± 5800 mcg•h per mL, 1.49 ± 2.13 mcg per mL, and 88.3 ± 41.4 mcg per mL, respectively. The accumulation ratios for AUC and C_{max} were 1.11 and 1.02, respectively. The accumulation ratio was higher for C_{min} (1.96). Steady-state was reached following the first administration for C_{max} and AUC, respectively, and after 16 weeks C_{min}.

For doses of ACTEMRA 8 mg per kg given every 4 weeks, the predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 35000 ± 15500 mcg•h per mL, 9.74 ± 10.5 mcg per mL, and 183 ± 85.6 mcg per mL, respectively. The accumulation ratios for AUC and C_{max} were 1.22 and 1.06, respectively. The accumulation ratio was higher for C_{min} (2.35). Steady-state was reached following the first administration and after 8 and 20 weeks for C_{max}, AUC, and C_{min}, respectively. Tocilizumab AUC, C_{min} and C_{max} increased with increase of body weight. At body weight at or above 100 kg, the predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 55500 ± 14100 mcg•h per mL, 19.0 ± 12.0 mcg per mL, and 269 ± 57 mcg per mL, respectively, which are higher than mean exposure values for the patient population. Therefore, ACTEMRA doses exceeding 800 mg per infusion are not recommended *[see Dosage and Administration (2.1)]*.

Systemic Juvenile Idiopathic Arthritis

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 75 patients with SJIA treated with 8 mg per kg (patients with a body weight at or above 30 kg) or 12 mg per kg (patients with a body weight less than 30 kg), given every 2 weeks. The predicted mean (± SD) $AUC_{2\ weeks}$, C_{max} and C_{min} of tocilizumab were 32200 ± 9960 mcg•hr per mL, 245 ± 57.2 mcg per mL and 57.5 ± 23.3 mcg per mL, respectively. The accumulation ratio for C_{min} (week 12 over week 2) was 3.2 ± 1.3. Steady state was reached on or after week 12. Mean predicted TCZ exposure parameters were similar between the two dose groups defined by body weight.

Distribution

Following intravenous dosing, tocilizumab undergoes biphasic elimination from the circulation. In rheumatoid arthritis patients the central volume of distribution was 3.5 L and the peripheral volume of distribution was 2.9 L, resulting in a volume of distribution at steady state of 6.4 L.

In pediatric patients with SJIA, the central volume of distribution was 0.94 L, the peripheral volume of distribution was 1.60 L resulting in a volume of distribution at steady state of 2.54 L.

Elimination

The total clearance of tocilizumab is concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance was estimated to be 12.5 mL per h in RA and 7.1 mL per h in pediatric patients with SJIA in the population pharmacokinetic analysis. The concentration-dependent nonlinear clearance plays a major role at low tocilizumab concentrations. Once the nonlinear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.

The $t_{1/2}$ of tocilizumab is concentration-dependent. The concentration-dependent apparent $t_{1/2}$ is up to 11 days for 4 mg per kg and up to 13 days for 8 mg per kg every 4 weeks in patients with RA at steady-state. The $t_{1/2}$ of tocilizumab in pediatric patients with SJIA is up to 23 days for the two body weight categories at week 12.

Pharmacokinetics in Special Populations

Population pharmacokinetic analyses in adult rheumatoid arthritis patients showed that age, gender and race did not affect the pharmacokinetics of tocilizumab. Linear clearance was found to increase with body size. The body weight-based dose (8 mg per kg) resulted in approximately 86% higher exposure in patients who are greater than 100 kg in comparison to patients who are less than 60 kg.

Hepatic Impairment

No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab was conducted.

Renal Impairment

No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab was conducted.

Most of the RA patients in the population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (creatinine clearance less than 80 mL per min and at or above 50 mL per min based on Cockcroft-Gault) did not impact the pharmacokinetics of tocilizumab. No dose adjustment is required in patients with mild renal impairment.

Drug Interactions

In vitro data suggested that IL-6 reduced mRNA expression for several CYP450 isoenzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and this reduced expression was reversed by co-incubation with tocilizumab at clinically relevant concentrations. Accordingly, inhibition of IL-6 signaling in RA patients treated with tocilizumab may restore CYP450 activities to higher levels than those in the absence of tocilizumab leading to increased metabolism of drugs that are CYP450 substrates. Its effect on CYP2C8 or transporters (e.g., P-gp) is unknown. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation of ACTEMRA, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) should be performed and the individual dose of the medicinal product adjusted as needed. Caution should be exercised when ACTEMRA is coadministered with drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives (CYP3A4 substrates) *[see Drug Interactions (7.2)]*.

Simvastatin

Simvastatin is a CYP3A4 and OATP1B1 substrate. In 12 RA patients not treated with ACTEMRA, receiving 40 mg simvastatin, exposures of simvastatin and its metabolite, simvastatin acid, was 4- to 10-fold and 2-fold

higher, respectively, than the exposures observed in healthy subjects. One week following administration of a single infusion of ACTEMRA (10 mg per kg), exposure of simvastatin and simvastatin acid decreased by 57% and 39%, respectively, to exposures that were similar or slightly higher than those observed in healthy subjects. Exposures of simvastatin and simvastatin acid increased upon withdrawal of ACTEMRA in RA patients. Selection of a particular dose of simvastatin in RA patients should take into account the potentially lower exposures that may result after initiation of ACTEMRA (due to normalization of CYP3A4) or higher exposures after discontinuation of ACTEMRA.

Omeprazole

Omeprazole is a CYP2C19 and CYP3A4 substrate. In RA patients receiving 10 mg omeprazole, exposure to omeprazole was approximately 2 fold higher than that observed in healthy subjects. In RA patients receiving 10 mg omeprazole, before and one week after ACTEMRA infusion (8 mg per kg), the omeprazole AUC_{inf} decreased by 12% for poor (N=5) and intermediate metabolizers (N=5) and by 28% for extensive metabolizers (N=8) and were slightly higher than those observed in healthy subjects.

Dextromethorphan

Dextromethorphan is a CYP2D6 and CYP3A4 substrate. In 13 RA patients receiving 30 mg dextromethorphan, exposure to dextromethorphan was comparable to that in healthy subjects. However, exposure to its metabolite, dextrorphan (a CYP3A4 substrate), was a fraction of that observed in healthy subjects. One week following administration of a single infusion of ACTEMRA (8 mg per kg), dextromethorphan exposure was decreased by approximately 5%. However, a larger decrease (29%) in dextrorphan levels was noted after ACTEMRA infusion.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis. No long-term animal studies have been performed to establish the carcinogenicity potential of tocilizumab.

Mutagenesis. Tocilizumab was negative in the in vitro Ames bacterial reverse mutation assay and the in vitro chromosomal aberrations assay using human peripheral blood lymphocytes.

Impairment of Fertility. Fertility studies conducted in male and female mice using a murine analogue of tocilizumab showed no impairment of fertility.

14 CLINICAL STUDIES

Rheumatoid Arthritis

The efficacy and safety of ACTEMRA was assessed in five randomized, double-blind, multicenter studies in patients greater than 18 years with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 8 tender and 6 swollen joints at baseline. ACTEMRA was given intravenously every 4 weeks as monotherapy (Study I), in combination with methotrexate (MTX) (Studies II and III) or other disease-modifying anti-rheumatic drugs (DMARDs) (Study IV) in patients with an inadequate response to those drugs, or in combination with MTX in patients with an inadequate response to TNF antagonists (Study V).

Study I evaluated patients with moderate to severe active rheumatoid arthritis who had not been treated with MTX within 24 weeks prior to randomization, or who had not discontinued previous methotrexate treatment as a result of clinically important toxic effects or lack of response. In this study, 67% of patients were MTX-naïve, and over 40% of patients had rheumatoid arthritis less than 2 years. Patients received ACTEMRA 8 mg per kg monotherapy or MTX alone (dose titrated over 8 weeks from 7.5 mg to a maximum of 20 mg weekly). The primary endpoint was the proportion of ACTEMRA patients who achieved an ACR20 response at Week 24.

Study II was a 104-week study with an ongoing optional 156-week extension phase that evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to MTX. Patients received ACTEMRA 8 mg per kg, ACTEMRA 4 mg per kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). Upon completion of 52-weeks, patients received open-label treatment with ACTEMRA 8 mg per kg through 104 weeks or they had the option to continue their double-blind treatment if they maintained a greater than 70% improvement in swollen/tender joint count. Two pre-specified interim analyses at week 24 and week 52 were conducted. The primary endpoint at week 24 was the proportion of patients who achieved an ACR20 response. At weeks 52 and 104, the primary endpoints were change from baseline in modified total Sharp-Genant score and the area under the curve (AUC) of the change from baseline in HAQ-DI score.

Study III evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to MTX. Patients received ACTEMRA 8 mg per kg, ACTEMRA 4 mg per kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Study IV evaluated patients who had an inadequate response to their existing therapy, including one or more DMARDs. Patients received ACTEMRA 8 mg per kg or placebo every four weeks, in combination with the stable DMARDs. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Study V evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response or were intolerant to one or more TNF antagonist therapies. The TNF antagonist therapy was discontinued prior to randomization. Patients received ACTEMRA 8 mg per kg, ACTEMRA 4 mg per kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Clinical Response

The percentages of ACTEMRA-treated patients achieving ACR20, 50 and 70 responses are shown in **Table 3.** In all studies, patients treated with 8 mg per kg ACTEMRA had higher ACR20, ACR50, and ACR70 response rates versus MTX- or placebo-treated patients at week 24.

During the 24 week controlled portions of Studies I to V, patients treated with ACTEMRA at a dose of 4 mg per kg in patients with inadequate response to DMARDs or TNF antagonist therapy had lower response rates compared to patients treated with ACTEMRA 8 mg per kg.

Table 3 Clinical Response at Weeks 24 and 52 in Active and Placebo Controlled Trials (Percent of Patients)

	Percent of Patients												
	Study I		Study II			Study III			Study IV		Study V		
	MTX	ACTEMRA 8 mg per kg	Placebo + MTX	ACTEMRA 4 mg per kg + MTX	ACTEMRA 8 mg per kg + MTX	Placebo + MTX	ACTEMRA 4 mg per kg + MTX	ACTEMRA 8 mg per kg + MTX	Placebo + DMARDs	ACTEMRA 8 mg per kg + DMARDs	Placebo + MTX	ACTEMRA 4 mg per kg + MTX	ACTEMRA 8 mg per kg + MTX
	N=284	N=286	N=393	N=399	N=398	N=204	N=213	N=205	N=413	N=803	N=158	N=161	N=170
Response Rate		(95% CI)[a]		(95% CI)[a]	(95% CI)[a]		(95% CI)[a]	(95% CI)[a]		(95% CI)[a]		(95% CI)[a]	(95% CI)[a]
ACR20													
Week 24	53%	70%	27%	51%	56%	27%	48%	59%	24%	61%	10%	30%	50%
		(0.11, 0.27)		(0.17, 0.29)	(0.23, 0.35)		(0.15, 0.32)	(0.23, 0.41)		(0.30, 0.40)		(0.15, 0.36)	(0.36, 0.56)
Week 52	N/A	N/A	25%	47%	56%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
				(0.15, 0.28)	(0.25, 0.38)								
ACR50													
Week 24	34%	44%	10%	25%	32%	11%	32%	44%	9%	38%	4%	17%	29%
		(0.04, 0.20)		(0.09, 0.20)	(0.16, 0.28)		(0.13, 0.29)	(0.25, 0.41)		(0.23, 0.33)		(0.05, 0.25)	(0.21, 0.41)
Week 52	N/A	N/A	10%	29%	36%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
				(0.14, 0.25)	(0.21, 0.32)								
ACR70													
Week 24	15%	28%	2%	11%	13%	2%	12%	22%	3%	21%	1%	5%	12%
		(0.07, 0.22)		(0.03, 0.13)	(0.05, 0.15)		(0.04, 0.18)	(0.12, 0.27)		(0.13, 0.21)		(-0.06, 0.14)	(0.03, 0.22)
Week 52	N/A	N/A	4%	16%	20%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
				(0.08, 0.17)	(0.12, 0.21)								
Major Clinical Responses[b]													
Week 52	N/A	N/A	1%	4%	7%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
				(0.01, 0.06)	(0.03, 0.09)								

[a] CI: 95% confidence interval of the weighted difference to placebo adjusted for site (and disease duration for Study I only)
[b] Major clinical response is defined as achieving an ACR 70 response for a continuous 24 week period

Table 4 Proportion of Patients with DAS28-ESR Less Than 2.6 with Number of Residual Active Joints

Study II			
	Placebo + MTX N = 393	**ACTEMRA 4 mg per kg + MTX N = 399**	**ACTEMRA 8 mg per kg + MTX N = 398**
DAS28-ESR less than 2.6			
Proportion of responders at week 52 (n) 95% confidence interval	3% (12)	18% (70) 0.10, 0.19	32% (127) 0.24, 0.34
Of responders, proportion with 0 active joints (n)	33% (4)	27% (19)	21% (27)
Of responders, proportion with 1 active joint (n)	8% (1)	19% (13)	13% (16)
Of responders, proportion with 2 active joints (n)	25% (3)	13% (9)	20% (25)
Of responders, proportion with 3 or more active joints (n)	33% (4)	41% (29)	47% (59)

*n denotes numerator of all the percentage. Denominator is the intent-to-treat population. Not all patients received DAS28 assessments at Week 52.

The results of the components of the ACR response criteria for Studies III and V are shown in **Table 5**. Similar results to Study III were observed in Studies I, II and IV.

Table 5 Components of ACR Response at Week 24

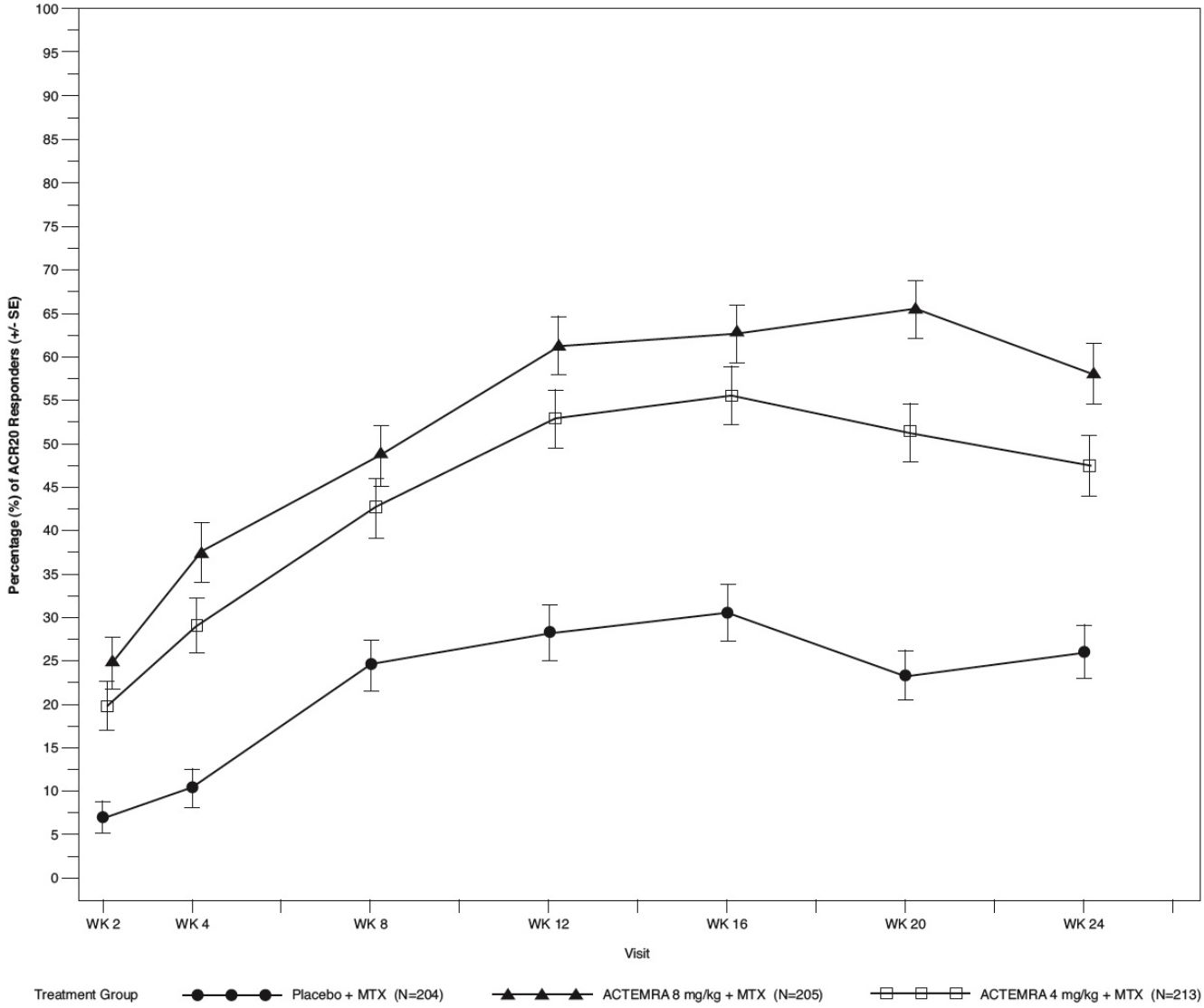
	Study III						Study V					
	ACTEMRA 4 mg per kg + MTX N=213		ACTEMRA 8 mg per kg + MTX N=205		Placebo + MTX N=204		ACTEMRA 4 mg per kg + MTX N=161		ACTEMRA 8 mg per kg + MTX N=170		Placebo + MTX N=158	
Component (mean)	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24**	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24**
Number of tender joints (0-68)	33	19 -7 0 (-10 0, -4 1)	32	14 5 -9 6 (-12 6, -6 7)	33	25	31	21 -10 8 (-14 6, -7 1)	32	17 -15 1 (-18 8, -11 4)	30	30
Number of swollen joints (0-66)	20	10 -4 2 (-6 1, -2 3)	19 5	8 -6 2 (-8 1, -4 2)	21	15	19 5	13 -6 2 (-9 0, -3 5)	19	11 -7 2 (-9 9, -4 5)	19	18
Pain[b]	61	33 -11 0 (-17 0, -5 0)	60	30 -15 8 (-21 7, -9 9)	57	43	63 5	43 -12 4 (-22 1, -2 1)	65	33 -23 9 (-33 7, -14 1)	64	48
Patient global assessment[b]	66	34 -10 9 (-17 1, -4 8)	65	31 -14 9 (-20 9, -8 9)	64	45	70	46 -10 0 (-20 3, 0 3)	70	36 -17 4 (-27 8, -7 0)	71	51
Physician global assessment[b]	64	26 -5 6 (-10 5, -0 8)	64	23 -9 0 (-13 8, -4 2)	64	32	66 5	39 -10 5 (-18 6, -2 5)	66	28 -18 2 (-26 3, -10 0)	67 5	43
Disability index (HAQ)[c]	1 64	1 01 -0 18 (-0 34, -0 02)	1 55	0 96 -0 21 (-0 37, -0 05)	1 55	1 21	1 67	1 39 -0 25 (-0 42, -0 09)	1 75	1 34 -0 34 (-0 51, -0 17)	1 70	1 58
CRP (mg per dL)	2 79	1 17 -1 30 (-2 0, -0 59)	2 61	0 25 -2 156 (-2 86, -1 46)	2 36	1 89	3 11	1 77 -1 34 (-2 5, -0 15)	2 80	0 28 -2 52 (-3 72, -1 32)	3 705	3 06

[a] Data shown is mean at week 24, difference in adjusted mean change from baseline compared with placebo + MTX at week 24 and 95% confidence interval for that difference
[b] Visual analog scale: 0 = best, 100 = worst

[c] Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities

The percent of ACR20 responders by visit for Study III is shown in **Figure 1**. Similar responses were observed in studies I, II, IV, and V.

Figure 1 Percent of ACR20 Responders by Visit for Study III (Inadequate Response to MTX)*



*The same patients may not have responded at each timepoint.

Radiographic Response

In Study II, structural joint damage was assessed radiographically and expressed as change in total Sharp-Genant score and its components, the erosion score and joint space narrowing score. Radiographs of hands/wrists and forefeet were obtained at baseline, 24 weeks, 52 weeks, and 104 weeks and scored by readers unaware of treatments group and visit number. The results from baseline to week 52 are shown in **Table 6**. ACTEMRA 4 mg per kg slowed (less than 75% inhibition compared to the control group) and ACTEMRA 8 mg per kg inhibited (at least 75% inhibition compared to the control group) the progression of structural damage compared to placebo plus MTX at week 52.

Table 6 Mean Radiographic Change from Baseline to Week 52 in Study II

	Placebo + MTX N=294	ACTEMRA 4 mg per kg + MTX N=343	ACTEMRA 8 mg per kg + MTX N=353
Week 52*			
Total Sharp-Genant Score, Mean (SD)	1.17 (3.14)	0.33 (1.30)	0.25 (0.98)
Adjusted Mean difference (95%CI)**		-0.83 (-1.13, -0.52)	-0.90 (-1.20, -0.59)
Erosion Score, Mean (SD)	0.76 (2.14)	0.20 (0.83)	0.15 (0.77)
Adjusted Mean difference (95%CI)**		-0.55 (-0.76, -0.34)	-0.60 (-0.80, -0.39)
Joint Space Narrowing Score, Mean (SD)	0.41 (1.71)	0.13 (0.72)	0.10 (0.49)
Adjusted Mean difference (95%CI)**		-0.28 (-0.44, -0.11)	-0.30 (-0.46, -0.14)

* Week 52 analysis employs linearly extrapolated data for patients after escape, withdrawal, or loss to follow up.
** Difference between the adjusted means (Actemra + MTX - Placebo + MTX)
SD = standard deviation

The mean change from baseline to week 104 in Total Sharp-Genant Score for the ACTEMRA 4 mg per kg groups was 0.47 (SD = 1.47) and for the 8 mg per kg groups was 0.34 (SD = 1.24). By the week 104, most patients in the control (placebo + MTX) group had crossed over to active treatment, and results are therefore not included for comparison. Patients in the active groups may have crossed over to the alternate active dose group, and results are reported per original randomized dose group.

In the placebo group, 66% of patients experienced no radiographic progression (Total Sharp-Genant Score change ≤ 0) at week 52 compared to 78% and 83% in the ACTEMRA 4 mg per kg and 8 mg per kg, respectively. Following 104 weeks of treatment, 75% and 83% of patients initially randomized to ACTEMRA 4 mg per kg and 8 mg per kg, respectively, experienced no progression of structural damage compared to 66% of placebo treated patients.

Health Related Outcomes

In Study II, physical function and disability were assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI). Both dosing groups of ACTEMRA demonstrated a greater improvement compared to the placebo group in the AUC of change from baseline in the HAQ-DI through week 52. The mean change from baseline to week 52 in HAQ-DI was 0.6, 0.5, and 0.4 for ACTEMRA 8 mg per kg, ACTEMRA 4 mg per kg, and placebo treatment groups, respectively. Sixty-three percent (63%) and sixty percent (60%) of patients in the ACTEMRA 8 mg per kg and ACTEMRA 4 mg per kg treatment groups, respectively, achieved a clinically relevant improvement in HAQ-DI (change from baseline of ≥ 0.3 units) at week 52 compared to 53% in the placebo treatment group.

Systemic Juvenile Idiopathic Arthritis (SJIA)

The efficacy of ACTEMRA for the treatment of active SJIA was assessed in a 12-week randomized, double blind, placebo-controlled, parallel group, 2-arm study. Patients treated with or without MTX, were randomized (ACTEMRA:placebo = 2:1) to one of two treatment groups: 75 patients received ACTEMRA infusions every two weeks at either 8 mg per kg for patients at or above 30 kg or 12 mg per kg for patients less than 30 kg and

37 were randomized to receive placebo infusions every two weeks. Corticosteroid tapering could occur from week six for patients who achieved a JIA ACR70 response. After 12 weeks or at the time of escape, due to disease worsening, patients were treated with ACTEMRA in the open-label extension phase at weight appropriate dosing.

The primary endpoint was the proportion of patients with at least 30% improvement in JIA ACR core set (JIA ACR30 response) at Week 12 and absence of fever (no temperature at or above 37.5°C in the preceding 7 days). JIA ACR (American College of Rheumatology) responses are defined as the percentage improvement (e.g., 30%, 50%, 70%) in 3 of any 6 core outcome variables compared to baseline, with worsening in no more than 1 of the remaining variables by 30% or more. Core outcome variables consist of physician global assessment, parent per patient global assessment, number of joints with active arthritis, number of joints with limitation of movement, erythrocyte sedimentation rate (ESR), and functional ability (childhood health assessment questionnaire-CHAQ).

Primary endpoint result and JIA ACR response rates at Week 12 are shown in **Table 7**.

Table 7 Efficacy Findings at Week 12

	ACTEMRA N=75	**Placebo N=37**
Primary Endpoint: JIA ACR 30 response + absence of fever		
Responders	**85%**	**24%**
Weighted difference (95% CI)	**62 (45, 78)**	**-**
JIA ACR Response Rates at Week 12		
JIA ACR 30		
Responders	91%	24%
Weighted difference[a]	67	-
(95% CI)[b]	(51, 83)	
JIA ACR 50		
Responders	85%	11%
Weighted difference[a]	74	-
(95% CI)[b]	(58, 90)	
JIA ACR 70		
Responders	71%	8%
Weighted difference[a]	63	-
(95% CI)[b]	(46, 80)	

[a]The weighted difference is the difference between the ACTEMRA and Placebo response rates, adjusted for the stratification factors (weight, disease duration, background oral corticosteroid dose and background methotrexate use).
[b] CI: confidence interval of the weighted difference.

The treatment effect of ACTEMRA was consistent across all components of the JIA ACR response core variables. JIA ACR scores and absence of fever responses in the open label extension were consistent with the controlled portion of the study (data available through 44 weeks).

Systemic Features

Of patients with fever or rash at baseline, those treated with ACTEMRA had fewer systemic features; 35 out of 41 (85%) became fever free (no temperature recording at or above 37.5°C in the preceding 14 days) compared to 5 out of 24 (21%) of placebo-treated patients, and 14 out of 22 (64%) became free of rash compared to 2 out of 18 (11%) of placebo-treated patients. Responses were consistent in the open label extension (data available through 44 weeks).

Corticosteroid Tapering

Of the patients receiving oral corticosteroids at baseline, 8 out of 31 (26%) placebo and 48 out of 70 (69%), ACTEMRA patients achieved a JIA ACR70 response at week 6 or 8 enabling corticosteroid dose reduction. Seventeen (24%) ACTEMRA patients versus 1 (3%) placebo patient were able to reduce the dose of corticosteroid by at least 20% without experiencing a subsequent JIA ACR30 flare or occurrence of systemic symptoms to week 12. In the open label portion of the study, by week 44, there were 44 out of 103 (43%) ACTEMRA patients off oral corticosteroids. Of these 44 patients 50% were off corticosteroids 18 weeks or more.

Health Related Outcomes

Physical function and disability were assessed using the Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI). Seventy-seven percent (58 out of 75) of patients in the ACTEMRA treatment group achieved a minimal clinically important improvement in CHAQ-DI (change from baseline of $\geq$ 0.13 units) at week 12 compared to 19% (7 out of 37) in the placebo treatment group.

16 HOW SUPPLIED/STORAGE AND HANDLING

ACTEMRA (tocilizumab) is supplied in single-use vials as a preservative-free, sterile concentrate (20 mg per mL) solution for intravenous infusion. The following packaging configurations are available:

Individually packaged, single-use vials:

NDC 50242-135-01 providing 80 mg per 4 mL

NDC 50242-136-01 providing 200 mg per 10 mL

NDC 50242-137-01 providing 400 mg per 20 mL

Box of 4 single-use vials:

NDC 50242-135-04 providing 80 mg per 4 mL

NDC 50242-136-04 providing 200 mg per 10 mL

NDC 50242-137-04 providing 400 mg per 20 mL

Storage and Stability: Do not use beyond expiration date on the container. ACTEMRA must be refrigerated at 2ºC to 8ºC (36°F to 46°F). Do not freeze. Protect the vials from light by storage in the original package until time of use. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particles are observed, the solution should not be used.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Patient Counseling

Patients and parents or guardians of minors with SJIA should be advised of the potential benefits and risks of ACTEMRA. Physicians should instruct their patients to read the Medication Guide before starting ACTEMRA therapy.

- **Infections:**
  Inform patients that ACTEMRA may lower their resistance to infections. Instruct the patient of the importance of contacting their doctor immediately when symptoms suggesting infection appear in order to assure rapid evaluation and appropriate treatment.
- **Gastrointestinal Perforation:**

Inform patients that some patients who have been treated with ACTEMRA have had serious side effects in the stomach and intestines. Instruct the patient of the importance of contacting their doctor immediately when symptoms of severe, persistent abdominal pain appear to assure rapid evaluation and appropriate treatment.

MEDICATION GUIDE

ACTEMRA® (AC-TEM-RA)

(tocilizumab)

Read this Medication Guide before you start ACTEMRA and before each infusion. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about ACTEMRA?

ACTEMRA can cause serious side effects including:

1. Serious Infections.

ACTEMRA is a medicine that affects your immune system. ACTEMRA can lower the ability of your immune system to fight infections. Some people have serious infections while taking ACTEMRA, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections.

Your doctor should test you for TB before starting ACTEMRA.

- Your doctor should monitor you closely for signs and symptoms of TB during treatment with ACTEMRA.

You should not start taking ACTEMRA if you have any kind of infection unless your healthcare provider says it is okay.

Before starting ACTEMRA, tell your healthcare provider if you:

- think you have an infection or have symptoms of an infection such as:
  - fever, sweating, or chills
  - muscle aches
  - cough
  - shortness of breath
  - blood in phlegm
  - weight loss
  - warm, red, or painful skin or sores on your body
  - diarrhea or stomach pain
  - burning when you urinate or urinating more often than normal
- feel very tired are being treated for an infection
- get a lot of infections or have infections that keep coming back
- have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB
- live or have lived, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections (histoplasmosis, coccidiomycosis, or blastomycosis). These infections may happen or become more severe if you use ACTEMRA. Ask your healthcare provider, if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B.

After starting ACTEMRA, call your healthcare provider right away if you have any symptoms of an infection. ACTEMRA can make you more likely to get infections or make worse any infection that you have.

2. Tears (perforation) of the stomach or intestines.

- Tell your healthcare provider if you have had diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people taking ACTEMRA get tears in their stomach or intestine. This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.
- Tell your healthcare provider right away if you have fever and stomach-area pain that does not go away, and a change in your bowel habits.

3. Changes in certain laboratory test results.

Your healthcare provider should do blood tests before you start receiving ACTEMRA and every 4 to 8 weeks for rheumatoid arthritis and every 2 to 4 weeks for SJIA during treatment to check for the following side effects of ACTEMRA:

- low neutrophil count. Neutrophils are white blood cells that help the body fight off bacterial infections.
- low platelet count. Platelets are blood cells that help with blood clotting and stop bleeding.
- increase in certain liver function tests.

You should not receive ACTEMRA if your neutrophil or platelet counts are too low or your liver function tests are too high.

Your healthcare provider may stop your ACTEMRA treatment for a period of time or change your dose of medicine if needed because of changes in these blood test results.

You may also have changes in other laboratory tests, such as your blood cholesterol levels. Your healthcare provider should do blood tests to check your cholesterol levels 4 to 8 weeks after you start receiving ACTEMRA, and then every 6 months after that. Normal cholesterol levels are important to good heart health.

4. Cancer.

ACTEMRA may increase your risk of certain cancers by changing the way your immune system works. Tell your healthcare provider if you have ever had any type of cancer.

See “What are the possible side effects with ACTEMRA?” for more information about side effects.

What is ACTEMRA?

ACTEMRA is a prescription medicine called an Interleukin-6 (IL-6) receptor inhibitor. ACTEMRA is used to treat:

- Adults with moderately to severely active rheumatoid arthritis (RA) after at least one other medicine called a Disease Modifying Anti-Rheumatic Drug (DMARD) has been used and did not work well.
- People with active systemic juvenile idiopathic arthritis (SJIA) ages 2 and above.

It is not known if ACTEMRA is safe and effective in children with SJIA under 2 years of age or in children with conditions other than SJIA.

Who should not take ACTEMRA?

Do not take ACTEMRA if you are allergic to tocilizumab, or any of the ingredients in ACTEMRA. See the end of this Medication Guide for a complete list of ingredients in ACTEMRA.

What should I tell my healthcare provider before receiving ACTEMRA?

ACTEMRA may not be right for you. **Before receiving ACTEMRA, tell your healthcare provider if you:**

- have an infection. See "What is the most important information I should know about ACTEMRA?"
- have liver problems
- have any stomach-area (abdominal) pain or been diagnosed with diverticulitis or ulcers in your stomach or intestines
- have had a reaction to tocilizumab or any of the ingredients in ACTEMRA before
- have or had a condition that affects your nervous system, such as multiple sclerosis
- have recently received or are scheduled to receive a vaccine. People who take ACTEMRA should not receive live vaccines. People taking ACTEMRA can receive non-live vaccines
- plan to have surgery or a medical procedure
- have any other medical conditions
- plan to become pregnant or are pregnant. It is not known if ACTEMRA will harm your unborn baby.

  Pregnancy Registry: Genentech has a registry for pregnant women who take ACTEMRA. The purpose of this registry is to check the health of the pregnant mother and her baby. If you are pregnant or become pregnant while taking ACTEMRA, talk to your healthcare provider about how you can join this pregnancy registry or you may contact the registry at 1-877-311-8972 to enroll.

- plan to breast-feed or are breast-feeding. You and your healthcare provider should decide if you will take ACTEMRA or breast-feed. You should not do both.

Tell your healthcare provider about all of the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. ACTEMRA and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:

- any other medicines to treat your RA. You should not take etanercept (Enbrel®), adalimumab (Humira®), infliximab (Remicade®), rituximab (Rituxan®), abatacept (Orencia®), anakinra (Kineret®), certolizumab (Cimzia®), or golimumab (Simponi®), while you are taking ACTEMRA. Taking ACTEMRA with these medicines may increase your risk of infection.
- medicines that affect the way certain liver enzymes work. Ask your healthcare provider if you are not sure if your medicine is one of these.

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How will I receive ACTEMRA?

- You will receive ACTEMRA from a healthcare provider through a needle placed in a vein in your arm (IV or intravenous infusion). The infusion will take about 1 hour to give you the full dose of medicine.

- For rheumatoid arthritis you will receive a dose of ACTEMRA about every 4 weeks.
- For SJIA you will receive a dose of ACTEMRA about every 2 weeks.
- If you miss a scheduled dose of ACTEMRA, ask your healthcare provider when to schedule your next infusion.
- While taking ACTEMRA, you may continue to use other medicines that help treat your rheumatoid arthritis or SJIA such as methotrexate, non-steroidal anti-inflammatory drugs (NSAIDs) and prescription steroids, as instructed by your healthcare provider.
- Keep all of your follow-up appointments and get your blood tests as ordered by your healthcare provider.

What are the possible side effects with ACTEMRA?

ACTEMRA can cause serious side effects, including:

- See "What is the most important information I should know about ACTEMRA?"
- **Hepatitis B infection** in people who carry the virus in their blood. If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus may become active while you use ACTEMRA. This happens with other biologic medicines used to treat RA. Your doctor may do blood tests before you start treatment with ACTEMRA and while you are using ACTEMRA. Tell your healthcare provider if you have any of the following symptoms of a possible hepatitis B infection:
    - feel very tired
    - skin or eyes look yellow
    - little or no appetite
    - vomiting
    - clay-colored bowel movements
    - fevers
    - chills
    - stomach discomfort
    - muscle aches
    - dark urine
    - skin rash

- **Serious Allergic Reactions.** Serious allergic reactions, including death, can happen with ACTEMRA. These reactions can happen with any infusion of ACTEMRA, even if they did not occur with an earlier infusion. Tell your healthcare provider right away if you have any of the following signs of a serious allergic reaction:
    - shortness of breath or trouble breathing
    - skin rash
    - swelling of the lips, tongue, or face
    - chest pain
    - feeling dizzy or faint

- **Nervous system problems.** Multiple Sclerosis has been diagnosed rarely in people who take ACTEMRA. It is not known what effect ACTEMRA may have on some nervous system disorders.

Common side effects of ACTEMRA include:

- upper respiratory tract infections (common cold, sinus infections)
- headache
- increased blood pressure (hypertension)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of ACTEMRA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Genentech at 1-888-835-2555.

General information about ACTEMRA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about ACTEMRA.

If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about ACTEMRA that is written for health professionals.

For more information, go to www.ACTEMRA.com or call 1-800-ACTEMRA.

What are the ingredients in ACTEMRA?

Active ingredient: tocilizumab

Inactive ingredients: sucrose, polysorbate 80, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

MG Revised: October 2012

ACTEMRA is a registered trademark of Chugai Seiyaku Kabushiki Kaisha Corp., a member of the Roche Group.

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