

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**BLA 125276/S049**

**REMS**

**Initial REMS Approved: 01/08/2010**

**Most Recent Modification: 10/2012**

**BLA 125276 ACTEMRA<sup>®</sup> (tocilizumab)**

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**Genentech, Inc.**

**A Member of the Roche Group**

**1 DNA Way**

**South San Francisco, CA 94080**

**I. GOALS**

The goal of the ACTEMRA REMS is:

- To inform healthcare providers about the serious risks associated with ACTEMRA.

**II. REMS ELEMENTS**

**A. Communication Plan (FDCA Section 505-1(e)(3))**

In accordance with FDCA 505-1(e)(3), Genentech, A Member of the Roche Group, will implement a communication plan to the following adult and pediatric healthcare providers:

- Rheumatologists and rheumatology healthcare providers who are likely to prescribe ACTEMRA
- Infectious disease specialists who may be consulted about serious infection
- Gastroenterologists and hepatologists who may be consulted about gastrointestinal perforation, hepatic disease, or hepatic impairment
- Family practitioners, general practitioners, osteopaths, internists, and internal medicine specialists who may be consulted about serious infections, gastrointestinal perforations, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, demyelinating disorders, and malignancies associated with ACTEMRA
- Emergency medicine specialists who may treat serious infections, gastrointestinal perforations, and changes in liver function
- Neurologists who may treat demyelinating disorders
- Oncologists who may treat malignancies

Elements of the communication plan include the following:

1. A Dear Healthcare Provider Letter (see **Attachment A**) will be distributed to adult and pediatric prescribers to include rheumatologists, gastroenterologists, hepatologists, neurologists, oncologists, infectious disease specialists, family medicine specialists, internal medicine specialists, emergency medicine specialists, and to infusion sites. This letter will be distributed within 60 days of approval of a new indication.

A Professional Label that includes the Medication Guide will also be distributed in this communication.

2. Prescriber Education Slide Deck

The prescriber education slide deck will provide information about specific safety risks (demyelination, malignancy, lipid elevations and monitoring advice and hypersensitivity reactions, including anaphylaxis) associated with ACTEMRA.

The slides will be available within 60 days of REMS modification approval through the following distribution methods:

- The [www. ACTEMRAREMS.com](http://www.ACTEMRAREMS.com) website (see **Attachment J** for the REMS Website landing page screenshot)
- Genentech Rheumatology Medical Science Liaison (MSL) will conduct educational sessions presenting these slides to rheumatology prescribers of ACTEMRA.
- Hard copy mailing, upon request, through Genentech's toll-free medical information line (1-800-228-3672)

The prescriber education slide deck will be available for 3 years following approval of the REMS Modification. The prescriber education slide deck is appended to this document (see **Attachment B**)

3. Dissemination of information about the known and potential risks associated with ACTEMRA to healthcare providers through certain professional societies' scientific meetings and journals:
  - a) For display as a panel/poster and distribution as printed material at major convention meetings of rheumatologists and other healthcare professionals specializing in rheumatology where the company has a sponsored booth for 2 years following product approval.
  - b) For quarterly presentation as a printed information piece in *Arthritis and Rheumatism*, *The Rheumatologist*, *Clinical Infectious Diseases*, *Clinical Gastroenterology and Hepatology*, *American Family Physician*, *Annals of Internal Medicine*, *Annals of Emergency Medicine*, *Neurology*, *Pediatrics*, *AAP (American Academy of Pediatrics) News*, and *Infectious Diseases in Children* for 3 years following product approval.
  - c) For quarterly presentation as a printed information piece in the *Journal of Clinical Oncology* for 5 years following product approval.

The REMS journal information pieces are appended to this document (see **Attachments C, D, E, F, G, H and I**).

4. Genentech will ensure that all materials listed in or appended to the ACTEMRA REMS program will be available through the ACTEMRA REMS program website [www.ACTEMRAREMS.com](http://www.ACTEMRAREMS.com) or by calling 1-800-228-3672. The ACTEMRA REMS program website will exist for 3 years following approval of the REMS Modification. The landing page for the ACTEMRA REMS program website is appended to this document (see **Attachment J**).

**B. Timetable for Submission of Assessments**

REMS assessments will be submitted to FDA at 18 months, 3 years, and 7 years after approval of the original REMS (January 8, 2010). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date so that it will be received by the FDA on or before the due date.

**ATTACHMENT A: DEAR HEALTHCARE PROVIDER LETTER**

[date]

## **IMPORTANT SAFETY INFORMATION Regarding ACTEMRA® (tocilizumab)**

Dear Healthcare Provider:

The purpose of this letter is to inform you of important safety information for ACTEMRA® (tocilizumab), an interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for two indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs) with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (sJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks.

The safety and efficacy of ACTEMRA® for conditions other than RA and sJIA have not yet been established.

ACTEMRA targets IL-6. FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for ACTEMRA to ensure that the benefits of the drug outweigh the potential risks of serious infections, gastrointestinal perforations, hypersensitivity reactions, including anaphylaxis, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, demyelinating disorders, and malignancies.

**You are advised to discuss the risks that may be associated with ACTEMRA therapy with patients and their caregivers.**

**The ACTEMRA Medication Guide must be provided to patients being treated with ACTEMRA or to their caregiver at the time of first dose or if the Medication Guide is materially changed. This Medication Guide contains information that can be used to facilitate discussions about the known and potential risks of therapy.**

### **IMPORTANT SAFETY INFORMATION ON KNOWN AND POTENTIAL RISKS**

#### ***Serious Infections***

- Patients treated with ACTEMRA are at increased risk for developing serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

- ACTEMRA should not be administered during an active infection, including localized infections. If a serious infection develops, ACTEMRA should be interrupted until the infection is controlled.
- Prior to initiating ACTEMRA, a test for latent TB should be performed. If the test is positive, treatment for TB should be started prior to starting ACTEMRA. All patients should be monitored for active TB during treatment, even if the initial latent TB test is negative.

### ***Gastrointestinal Perforations***

- Events of gastrointestinal (GI) perforations have been reported in Phase 3 clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate
- During the six-month Phase 3 clinical trials, the overall rate of GI perforations was 0.26 events per 100 patient-years with ACTEMRA therapy versus no events for control.
- ACTEMRA should be used with caution in patients who may be at increased risk for GI perforation. Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

### ***Hypersensitivity Reactions, Including Anaphylaxis***

- Hypersensitivity reactions, including anaphylaxis and death, have been reported in association with infusion of ACTEMRA.
- Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials, 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.
- ACTEMRA should only be infused 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.

### ***Potential Risk of Demyelinating Disorders***

- The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies of adults with RA. 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.

### ***Potential Risk of Malignancies***

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

## **IMPORTANT INFORMATION ON LABORATORY ABNORMALITIES**

Hepatic transaminases, lipids, neutrophils and platelets should be monitored, as abnormalities in these parameters were associated with ACTEMRA treatment in Phase 3 clinical trials. Prior to initiating treatment with ACTEMRA, it is recommended that appropriate baseline laboratory parameters be measured. While on ACTEMRA, liver aminotransferases (ALT, AST), neutrophil counts, and platelet counts should be measured every 4 to 8 weeks for RA and at the time of the second infusion and, thereafter, every 2 to 4 weeks for sJIA. Total cholesterol and low-density lipoproteins should be measured 4 to 8 weeks after the first infusion and every 6 months thereafter for both RA and sJIA. Dosage modifications may be required if laboratory abnormalities occur. Please see the accompanying full Prescribing Information for more information.

## **REPORTING ADVERSE EVENTS**

It is important that you report all serious adverse events that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. The information you provide about these events may inform therapy and monitoring decisions.

**Reporting is easy and maintains patient confidentiality.** Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

## **FULL PRESCRIBING INFORMATION AND MEDICATION GUIDE**

This letter is not a comprehensive description of the risks associated with the use of ACTEMRA. Please read the accompanying full Prescribing Information that includes the Medication Guide for a complete description of these risks.

This Medication Guide contains information that can be used to facilitate discussions about the known and potential risks of therapy.

Should you require additional copies of the ACTEMRA Medication Guide, you may:

- Request copies from Genentech by calling the toll-free medical information line at 1-800-ACTEMRA (1-800-228-3672)
- Print copies of the Medication Guide from the ACTEMRA Web site at [www.ACTEMRA.com](http://www.ACTEMRA.com)

For more information, please call 1-800-ACTEMRA or visit [www.ACTEMRA.com](http://www.ACTEMRA.com)

Sincerely,

Hal Barron, MD  
Chief Medical Officer, USA  
Genentech, Inc.

Enclosure

## **ATTACHMENT B: PRESCRIBER EDUCATION SLIDE DECK**

# ACTEMRA Risk Mitigation Strategy

*Presenter Name, Degree  
Medical Science Liaison  
Genentech, Inc*

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## Overview of AEs of Special Interest

- Serious Adverse Events
- Infections, serious infections and opportunistic infections
- Gastrointestinal perforations
- Decreases in peripheral neutrophil counts and decreases in platelet counts
- Changes in liver function tests
- Cardiovascular events and elevated lipid parameters
- Malignancies
- Hypersensitivity reactions, including anaphylaxis
- Demyelinating disorders

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## ACTEMRA: Boxed Warning

### **WARNING: RISK OF SERIOUS INFECTIONS**

*See full prescribing information for complete boxed warning.*

- Serious infections leading to hospitalization or death including tuberculosis (TB), bacteria, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving ACTEMRA.
- If a serious infection develops, interrupt ACTEMRA until the infection is controlled.
- Perform tests for latent TB; if positive, start treatment for TB prior to starting ACTEMRA.
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative.

## ACTEMRA: Warnings and Precautions

- 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.
- ACTEMRA should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis.

## Lipids: Warnings and Precautions

### *Rheumatoid Arthritis*

- Treatment with ACTEMRA was associated with increases in lipid parameters such as:
  - Total cholesterol
  - Triglycerides
  - LDL cholesterol
  - HDL cholesterol
- **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 for the management of hyperlipidemia.
- Prescribers should exercise caution when ACTEMRA is coadministered with CYP3A4 substrate drugs where decrease in effectiveness is undesirable (e.g., simvastatin, lovastatin, atorvastatin, etc.).

## Hypersensitivity Reactions, Including Anaphylaxis: Warnings and Precautions

- Hypersensitivity reactions, including anaphylaxis and death, have been reported in association with infusion of ACTEMRA.
- Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials, 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.
- ACTEMRA should only be infused 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.

## ACTEMRA: Warnings and Precautions

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

ACTEMRA Prescribing Information, mm/yyyy

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## ACTEMRA: Warnings and Precautions

- 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.

ACTEMRA Prescribing Information, mm/yyyy

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## ACTEMRA: Warnings and Precautions

- 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.

ACTEMRA Prescribing Information, mm/yyyy

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## Liver Enzyme Abnormalities: Monitoring and Dosage Modifications

- It is recommended that ACTEMRA **NOT** be initiated in patients who have ALT or AST above 1.5 times the upper limit of normal (ULN).
- 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.

### Elevated Liver Enzyme

| ALT or AST values                               | Recommendation   |
|---|--|
| > 1 to 3 x ULN                                  | Dose modify concomitant DMARDs if appropriate<br><br>For persistent increases in this range, reduce ACTEMRA dose to 4 mg per kg or interrupt ACTEMRA until ALT or AST have normalized  |
| > 3 to 5 x ULN<br>(confirmed by repeat testing) | Interrupt ACTEMRA dosing until less than 3x ULN and follow recommendations above for greater than 1 to 3x ULN<br><br>For persistent increases greater than 3x ULN, discontinue ACTEMRA |
| > 5 x ULN                                       | Discontinue ACTEMRA  |

ACTEMRA Prescribing Information, mm/yyyy

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## Neutrophils: Monitoring and Dosage Modifications

- It is recommended that ACTEMRA **NOT** be initiated in patients with an absolute neutrophil count (ANC) below 2000 per mm<sup>3</sup>.
- Neutrophils should be monitored every 4 to 8 weeks.

### Neutropenia Risk Mitigation

| ANC (cells/mm <sup>3</sup> ) | Recommendation   |
|------------------------------|--|
| > 1000                       | Maintain Dose  |
| 500 – 1000                   | Interrupt ACTEMRA dosing<br><br>When ANC greater than 1000 cells per mm <sup>3</sup> resume TCZ at 4 mg per kg and increase to 8 mg per kg as clinically appropriate |
| < 500                        | Discontinue ACTEMRA  |

## Platelets: Monitoring and Dosage Modifications

- It is recommended that ACTEMRA **NOT** be initiated in patients with a platelet count < 100,000/mm<sup>3</sup>.
- Platelets should be monitored every 4 to 8 weeks.

### Thrombocytopenia Risk Mitigation

| Platelet count (cells/mm <sup>3</sup> ) | Recommendation  |
|---|---|
| 50,000 – 100,000                        | Interrupt ACTEMRA dosing<br><br>When platelet count is greater than 100,000 cells per mm <sup>3</sup> resume ACTEMRA at 4 mg per kg and increase to 8 mg per kg as clinically appropriate |
| < 50,000                                | Discontinue ACTEMRA   |



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**ATTACHMENT C: JOURNAL INFORMATION PIECE FOR  
EMERGENCY MEDICINE PHYSICIANS AND EMERGENCY  
MEDICAL SERVICES PROFESSIONALS**

## Important Safety Information for Emergency Medicine Physicians About Potential Risks of Infection and Gastrointestinal Perforation With ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for two indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs) with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (sJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks.

The safety and efficacy of ACTEMRA® for conditions other than RA and sJIA have not yet been established.

**Emergency medicine physicians** should be aware of important safety information regarding ACTEMRA®.

**Serious infections:** Patients treated with ACTEMRA are at increased risk for developing serious infections leading to hospitalization or death. These infections include tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections.

**Gastrointestinal perforations:** Gastrointestinal (GI) perforations have been reported in Phase 3 clinical trials, primarily as complications of diverticulitis. Reported perforations have involved generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate. Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

In addition to these adverse events, patients treated with ACTEMRA may have elevated hepatic transaminases (ALT, AST) and lipids, and decreased neutrophils and platelet counts. Dosage modifications may be required if laboratory abnormalities occur. Please see the full Prescribing Information for more information.

**Hypersensitivity reactions, including anaphylaxis:** Hypersensitivity reactions, including anaphylaxis and death, have been reported in association with infusion of ACTEMRA. Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials, 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.

ACTEMRA should only be infused 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.

Please see full Prescribing Information for more information.

### ***Reporting Adverse Events***

It is important that you report all serious adverse events that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. The information that you provide about these events may inform therapy and monitoring decisions for future patients.

**Reporting is easy and maintains patient confidentiality.** Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

**Please visit [www.ACTEMRA.com](http://www.ACTEMRA.com) for full Prescribing Information and Medication Guide.**

**ATTACHMENT D: JOURNAL INFORMATION PIECE FOR  
GASTROENTEROLOGISTS AND HEPATOLOGISTS**

## Important Safety Information for Gastroenterologists and Hepatologists About Potential Risks of Gastrointestinal Perforation and Transaminase Elevations With ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for two indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs) with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (sJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks.

The safety and efficacy of ACTEMRA® for conditions other than RA and sJIA have not yet been established.

**Gastroenterologists** and **hepatologists** should be aware of important safety information regarding ACTEMRA.

**Gastrointestinal perforations:** Gastrointestinal (GI) perforations have been reported in Phase 3 clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate. ACTEMRA should be used with caution in patients who may be at increased risk for GI perforation. Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

**Transaminase elevations:** Treatment with ACTEMRA was associated with a higher incidence of transaminase elevations (ALT, AST) in Phase 3 clinical trials. These elevations did not result in apparent permanent or clinically evident hepatic injury with modification of the treatment regimen, which resulted in a decrease or normalization of liver enzymes. Patients receiving ACTEMRA should be monitored for elevated transaminase levels and dose modifications may be necessary. When clinically indicated, other liver function tests, such as bilirubin, should be considered. Please see the full Prescribing Information for more information.

### **Reporting Adverse Events**

It is important that you report any serious gastrointestinal adverse events, including GI perforation, hepatic disease or hepatic impairment, that occur in a patient being treated with ACTEMRA, even if you do not think there is a causal relationship. The information that you, as a gastroenterologist or hepatologist, provide about these events may inform therapy and monitoring decisions for future patients.

**Reporting is easy and maintains patient confidentiality.** Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

**Please visit [www.ACTEMRA.com](http://www.ACTEMRA.com) for full Prescribing Information and Medication Guide.**

**ATTACHMENT E: JOURNAL INFORMATION PIECE FOR  
INFECTIOUS DISEASE SPECIALISTS**

## Important Safety Information for Infectious Disease Specialists About Potential Risks of Infections With ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for two indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs) with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (sJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks.

The safety and efficacy of ACTEMRA® for conditions other than RA and sJIA have not yet been established.

**Infectious disease specialists** should be aware of important safety information regarding ACTEMRA.

**Serious infections:** Patients treated with ACTEMRA are at increased risk for developing serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections.

ACTEMRA should not be administered during an active infection, including localized infections. If a serious infection develops, ACTEMRA should be interrupted until the infection is controlled.

### **Reporting Adverse Events**

It is important that you report all serious infections that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. The information that you, as an infectious disease specialist, provide about these events may inform therapy and monitoring decisions for future patients.

**Reporting is easy and maintains patient confidentiality.** Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

**Please visit [www.ACTEMRA.com](http://www.ACTEMRA.com) for full Prescribing Information and Medication Guide.**

**ATTACHMENT F: JOURNAL INFORMATION PIECE FOR  
INTERNISTS AND INTERNAL MEDICINE SUBSPECIALISTS**

## Important Safety Information for Physicians About Risks in Patients Receiving ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for two indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs) with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (sJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks.

The safety and efficacy of ACTEMRA® for conditions other than RA and sJIA have not yet been established.

**Physicians** should be aware of important information regarding safety and laboratory monitoring recommendations for ACTEMRA.

**Serious infections:** Patients treated with ACTEMRA are at increased risk for developing serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections.

**Gastrointestinal perforations:** Gastrointestinal (GI) perforations have been reported in Phase 3 clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate. ACTEMRA should be used with caution in patients who may be at increased risk for GI perforation. Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

**Hypersensitivity reactions, Including anaphylaxis:** Hypersensitivity reactions, including anaphylaxis and death, have been reported in association with infusion of ACTEMRA. Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials, 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.

ACTEMRA should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis. Please see full Prescribing Information for more information.

**Demyelinating disorders:** The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies of adults with RA. 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.

**Malignancies:** Malignancies were observed in clinical studies of ACTEMRA. The impact of treatment with ACTEMRA on the development of the malignancies is not known, but malignancy is a known risk of biological products that suppress the immune system. ACTEMRA is an immunosuppressant and may increase the risk of malignancies.

**Laboratory abnormalities:** Hepatic transaminases (ALT, AST), lipids, neutrophils, and platelets should be monitored, as abnormalities in these parameters were associated with ACTEMRA treatment in Phase 3 clinical trials. Dosage modifications may be required if laboratory abnormalities occur. Please see the full Prescribing Information for more information.

### ***Reporting Adverse Events***

It is important that you report all serious adverse events that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. As an ACTEMRA-prescribing internist and/or internal medicine subspecialist, such as a rheumatologist, the information you provide about these events may inform therapy and monitoring decisions for future patients.

**Reporting is easy and maintains patient confidentiality.** Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

**Please visit [www.ACTEMRA.com](http://www.ACTEMRA.com) for full Prescribing Information and Medication Guide.**

**ATTACHMENT G: JOURNAL INFORMATION PIECE FOR  
NEUROLOGISTS**

## Important Safety Information for Neurologists About Demyelinating Disorders in Co-managing Rheumatoid Arthritis Patients Receiving ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for two indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs) with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (sJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks.

The safety and efficacy of ACTEMRA® for conditions other than RA and sJIA have not yet been established.

**Neurologists** co-managing RA patients should be aware of important safety information regarding treatment with ACTEMRA.

**Demyelinating disorders:** The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies of adults with RA. 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.

### ***Reporting Adverse Events***

It is important that you report any serious neurologic adverse event, including demyelinating disorders, that occurs in a patient being treated with ACTEMRA, even if you do not think there is a causal relationship. The information that you, as a neurologist, provide about these events may inform therapy and monitoring decisions for future patients.

**Reporting is easy and maintains patient confidentiality.** Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

**Please visit [www.ACTEMRA.com](http://www.ACTEMRA.com) for full Prescribing Information and Medication Guide.**

**ATTACHMENT H: JOURNAL INFORMATION PIECE FOR  
ONCOLOGISTS**

## Important Safety Information for Oncologists About Malignancy Risk With ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for two indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs) with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (sJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks.

The safety and efficacy of ACTEMRA® for conditions other than RA and sJIA have not yet been established.

**Oncologists** should be aware of important safety information about ACTEMRA.

**Malignancies** were observed in clinical studies of ACTEMRA. The impact of treatment with ACTEMRA on the development of the malignancies is not known, but malignancy is a known risk of biological products that suppress the immune system. ACTEMRA is an immunosuppressant and may increase the risk of malignancies.

### ***Reporting Adverse Events***

If you are consulted to see a patient with cancer at any time after receiving ACTEMRA therapy, it is important that you report the case, even if you do not think there is a causal relationship. The information that you, as an oncologist, provide about these events may inform therapy and monitoring decisions for future patients.

**Reporting is easy and maintains patient confidentiality.** Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

**Please visit [www.ACTEMRA.com](http://www.ACTEMRA.com) for full Prescribing Information and Medication Guide.**

**ATTACHMENT I: JOURNAL INFORMATION PIECE FOR  
RHEUMATOLOGISTS**

## Important Safety Information for Rheumatologists About Risks in Patients Receiving ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for two indications:

- Adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs) with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (sJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks.

The safety and efficacy of ACTEMRA® for conditions other than RA and sJIA have not yet been established.

**Rheumatologists** should be aware of important information regarding safety and laboratory monitoring recommendations for ACTEMRA.

**Serious infections:** Patients treated with ACTEMRA are at increased risk for developing serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral and other opportunistic infections.

**Gastrointestinal perforations:** Gastrointestinal (GI) perforation have been reported in Phase 3 clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate. ACTEMRA should be used with caution in patients who may be at increased risk for GI perforation. Patients presenting with new-onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

**Demyelinating disorders:** The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies of adults with RA. 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.

**Malignancies:** Malignancies were observed in clinical studies of ACTEMRA. The impact of treatment with ACTEMRA on the development of the malignancies is not known, but malignancy is a known risk of biological products that suppress the immune system. ACTEMRA is an immunosuppressant and may increase the risk of malignancies.

**Laboratory abnormalities:** Hepatic transaminases (ALT, AST), lipids, neutrophils and platelets should be monitored, as abnormalities in these parameters were associated with ACTEMRA treatment in Phase 3 clinical trials. Dosage modifications may be required if laboratory abnormalities occur. Please see the full Prescribing Information for more information.

***Reporting Adverse Events***

It is important that you report all serious adverse events that occur in patients being treated with ACTEMRA, even if you do not think there is a causal relationship. As an ACTEMRA-prescribing rheumatologist, the information you provide about these events may inform therapy and monitoring decisions for future patients.

**Reporting is easy and maintains patient confidentiality.** Your patient's name or contact information is not needed. *HIPAA does not apply to this adverse event reporting.* You can report your cases to Genentech or directly to the FDA:

- Genentech at 1-800-ACTEMRA (1-800-228-3672)
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

**Please visit [www.ACTEMRA.com](http://www.ACTEMRA.com) for full Prescribing Information and Medication Guide.**

**ATTACHMENT J: ACTEMRA REMS WEBSITE SCREENSHOT**



## Risk Evaluation and Mitigation Strategy (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits outweigh its risks.

To learn more about serious risks, read the [Important Safety Information](#) and [Medication Guide](#) and discuss it with your patients.

The goal of the ACTEMRA REMS is:

- To inform healthcare providers about the serious risks associated with ACTEMRA.

Genentech recommends laboratory monitoring of patients being treated with ACTEMRA due to the potential consequences of treatment-related abnormalities in liver function, lipids, neutrophils and platelets. If you become aware of a patient who has developed a serious adverse event while being treated with ACTEMRA, it is important that you report the case, even if you do not think there is a causal relationship. The information you provide about these events may inform therapy and monitoring decisions.

Continue to check back on this Web site, it will be updated to include additional information intended to assist in the proper communication of the risks and benefits of ACTEMRA.

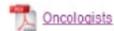
### Prescriber Education Slide Deck



### Healthcare Professional Letter



### Journal Information Pieces



For more information on safety, please [click here](#).

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SALLY M SEYMOUR  
10/11/2012