Initial REMS Approved: 01/08/2010

Most Recent Modification: October/2013

BLA 125276 and BLA 125472

ACTEMRA® (tocilizumab)

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Genentech, Inc.

A Member of the Roche Group

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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

Reference ID: 3394610

- 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 or new dosage form.

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 (including, but not limited to, demyelination, malignancy, laboratory parameters and dosage modifications, 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 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 (completed January 2012).

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 (completed January 2013).

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c) For quarterly presentation as a printed information piece in the *Journal of Clinical Oncology* for 5 years following product approval (through January 2015).

The REMS journal information piece is 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 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, 5 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.

Reference ID: 3394610

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 antagonist that has been approved by the Food and Drug Administration (FDA) for three 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 for intravenous (IV) or every other week or weekly for subcutaneous (SC) administration.

- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA® dosing interval of every 4 weeks for IV administration.

- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks for IV administration.

The safety and efficacy of ACTEMRA® for conditions other than RA, PJIA, 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.
- Avoid ACTEMRA during an active infection, including localized infections. If a serious infection develops, hold ACTEMRA until the infection is controlled.
- Prior to initiating ACTEMRA, test for latent TB infection. If the test is positive, initiate treatment for TB prior to starting ACTEMRA. Monitor all patients 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 RA clinical trials, the overall rate of GI perforations was 0.26 events per 100 patient-years with intravenous ACTEMRA therapy versus no events for control.
- Use ACTEMRA with caution in patients who may be at increased risk for GI perforation. Promptly evaluate patients presenting with new-onset abdominal symptoms for early identification of GI perforation.

Hypersensitivity Reactions, Including Anaphylaxis

- Hypersensitivity reactions, including anaphylaxis, have been reported in association with ACTEMRA and anaphylactic events with a fatal outcome have been reported with intravenous infusion of ACTEMRA.
- Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials of intravenous ACTEMRA, 0.2% (8 out of 4009) of patients in the intravenous all-exposure RA population, 0.7% (8 out of 1068) in the subcutaneous 6-month controlled RA trials, and in 0.7% (10 out of 1465) of patients in the subcutaneous all-exposure population.
- In the SJIA controlled trial with intravenous ACTEMRA, 1 out of 112 patients (0.9%) experienced hypersensitivity reactions that required treatment discontinuation. In the PJIA controlled trial with intravenous ACTEMRA 0 out of 188 patients (0%) in the all-exposure population experienced hypersensitivity reactions that required treatment discontinuation. Reactions that required treatment discontinuation included generalized erythema, rash, urticaria. Injection site reactions were categorized separately.
- In the postmarketing setting, events of hypersensitivity reactions, including anaphylaxis and death have occurred in patients treated with a range of doses of intravenous ACTEMRA, with or without concomitant arthritis therapies. Events have occurred in patients who received premedication. Hypersensitivity,

including anaphylaxis events, have occurred both with and without previous hypersensitivity reactions and as early as the first infusion of ACTEMRA.

- ACTEMRA for intravenous use should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis. For ACTEMRA subcutaneous injection, advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, stop administration of ACTEMRA immediately and discontinue ACTEMRA permanently. Do not administer ACTEMRA to patients with known hypersensitivity to ACTEMRA.

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

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, monitor liver aminotransferases (ALT, AST), neutrophil counts, and platelet counts 4 to 8 weeks after start of therapy and every 3 months thereafter for RA, at the time of the second infusion and, thereafter, every 4 to 8 weeks for PJIA, and at the time of the second infusion and, thereafter, every 2 to 4 weeks for SJIA. Assess total cholesterol and low-density lipoproteins 4 to 8 weeks after the first infusion and every 6 months thereafter for RA, PJIA and SJIA. Dosage modifications may be required if laboratory abnormalities occur.

Please see the accompanying 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 1-888-835-2555
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

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 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

For more information, please call 1-800-ACTEMRA or visit www.ACTEMRAREMS.com

Sincerely,

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

Enclosure
Version: October 2013

ATTACHMENT B: PRESCRIBER EDUCATION SLIDE DECK

ACTEMRA Risk Mitigation Strategy

Presenter Name, Degree

Medical Science Liaison
Genentech, Inc.

Version: 10/2013

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Reference ID: 3394610

Indications and Dosage
Rheumatoid Arthritis (RA) (1 of 2)

Indication in RA

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

Dosage in RA

- ACTEMRA may be used as monotherapy or concomitantly with methotrexate or other non-biologic DMARDs.

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Indications and Dosage
Rheumatoid Arthritis (RA) (2 of 2)

Recommended Intravenous (IV) Dosage Regimen in RA

- The recommended dosage of ACTEMRA for adult patients given as a 60-minute single IV 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.
- Doses exceeding 800 mg per infusion are not recommended in RA patients.

Recommended Subcutaneous (SC) Dosage Regimen in RA

Patients less than 100 kg weight	162 mg administered SC every other week, followed by an increase to every week based on clinical response
Patients at or above 100 kg weight	162 mg administered SC every week

- When transitioning from ACTEMRA IV therapy to SC administration, administer the first SC dose instead of the next scheduled IV dose.

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Indications and Dosage
Polyarticular Juvenile Idiopathic Arthritis (PJIA)

Indication in PJIA

- ACTEMRA (tocilizumab) is indicated for the treatment of active PJIA in patients 2 years of age and older.

Dosage in PJIA

- ACTEMRA may be used alone or in combination with methotrexate.

Recommended IV PJIA Dosage Every 4 Weeks (as a 60-minute single IV drip infusion)	
Patients less than 30 kg weight	10 mg/kg
Patients at or above 30 kg weight	8 mg/kg

- SC administration is not approved for PJIA.

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Indications and Dosage
Systemic Juvenile Idiopathic Arthritis (SJIA)

Indication in SJIA

- ACTEMRA (tocilizumab) is indicated for the treatment of active SJIA in patients 2 years of age and older.

Dosage in SJIA

- ACTEMRA may be used alone or in combination with methotrexate.

Recommended IV SJIA Dosage Every 2 Weeks (as a 60-minute single IV drip infusion)	
Patients less than 30 kg weight	12 mg/kg
Patients at or above 30 kg weight	8 mg/kg

- SC administration is not approved for SJIA.

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Overview of Adverse Events of Special Interest

- Serious Infections
- Gastrointestinal Perforations
- Laboratory Parameters
  - Low absolute neutrophil count
  - Reduction in platelet count
  - Elevations in liver function tests
  - Increases in lipid parameters
- Immunosuppression and Malignancies
- Hypersensitivity Reactions, Including Anaphylaxis
- Demyelinating Disorders

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Boxed Warning
Serious Infections

Do not administer ACTEMRA in patients with an active infection, including localized infections.

Important Information

- Patients treated with ACTEMRA are at increased risk for developing serious infections that may lead to hospitalization or death.
- Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Recommendation in RA, PJIA, and SJIA

- If a serious infection develops, interrupt ACTEMRA until infection is controlled.
- 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.

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Warnings and Precautions
Gastrointestinal Perforations

Important Information

- Events of gastrointestinal perforation have been reported in clinical trials, primarily as complications of diverticulitis in RA patients.

Recommendation in RA, PJIA, and SJIA

- Use ACTEMRA with caution in patients who may be at increased risk for gastrointestinal perforation.
- Promptly evaluate patients presenting with new onset abdominal symptoms for early identification of gastrointestinal perforation.

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Warnings and Precautions
Laboratory Parameters: Neutropenia

Important Information
• 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.

Recommendation in RA	Recommendation in PJIA	Recommendation in SJIA
• It is **NOT** recommended to initiate ACTEMRA treatment in patients with an absolute neutrophil count (ANC) below 2000 per mm^3. • Monitor neutrophils 4 to 8 weeks after start of therapy and every 3 months thereafter.	• It is **NOT** recommended to initiate ACTEMRA treatment in patients with an absolute neutrophil count (ANC) below 2000 per mm^3. • Monitor neutrophils at the **time of the second infusion and thereafter every 4 to 8 weeks.**	• It is **NOT** recommended to initiate ACTEMRA treatment in patients with an absolute neutrophil count (ANC) below 2000 per mm^3. • Monitor neutrophils at the **time of the second infusion and thereafter every 2 to 4 weeks.**

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Dosage Modifications
Low Absolute Neutrophil Count (ANC)

ANC (cells/mm³)	Recommendation in RA	Recommendation in PJIA and SJIA
>1000	• Maintain ACTEMRA dose	• Maintain ACTEMRA dose
500-1000	• Hold ACTEMRA dosing • When ANC greater than 1000 cells per mm³: - For patients receiving IV ACTEMRA, resume ACTEMRA at 4 mg per kg and increase to 8 mg per kg as clinically appropriate. - For patients receiving SC ACTEMRA, resume ACTEMRA at every other week and increase frequency to every week as clinically appropriate.	• Dose interruptions of ACTEMRA are recommended for low neutrophil counts at levels similar to what is outlined for patients with RA. • If appropriate, dose modify or stop concomitant MTX and/or other medications. • Hold ACTEMRA dosing until the clinical situation has been evaluated.
<500	• Discontinue ACTEMRA	• The decision to discontinue ACTEMRA for a laboratory abnormality should be based on the medical assessment of the individual patient.

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Warnings and Precautions
Laboratory Parameters: Thrombocytopenia

Important Information
• 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.

Recommendation in RA	Recommendation in PJIA	Recommendation in SJIA
• It is **NOT** recommended to initiate ACTEMRA treatment in patients with a platelet count <100,000/mm³. • Monitor platelets 4 to 8 weeks after start of therapy and every 3 months thereafter.	• It is **NOT** recommended to initiate ACTEMRA treatment in patients with a platelet count <100,000/mm³. • Monitor platelets at the **time of the second infusion and thereafter every 4 to 8 weeks.**	• It is **NOT** recommended to initiate ACTEMRA treatment in patients with a platelet count <100,000/mm³. • Monitor platelets at the **time of the second infusion and thereafter every 2 to 4 weeks.**

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Dosage Modifications
Low Platelet Count

Platelet Count (cells/mm³)	Recommendation in RA	Recommendation in PJIA and SJIA
50,000 – 100,000	• Hold ACTEMRA dosing • When platelet count is greater than 100,000 cells per mm³: - For patients receiving IV ACTEMRA, resume ACTEMRA at 4 mg per kg and increase to 8 mg per kg as clinically appropriate. - For patients receiving SC ACTEMRA, resume ACTEMRA at every other week and increase frequency to every week as clinically appropriate.	• Dose interruptions of ACTEMRA are recommended for low platelet counts at levels similar to what is outlined for patients with RA. • If appropriate, dose modify or stop concomitant MTX and/or other medications. • Hold ACTEMRA dosing until the clinical situation has been evaluated.
<50,000	• Discontinue ACTEMRA	• The decision to discontinue ACTEMRA for a laboratory abnormality should be based on the medical assessment of the individual patient.

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Warnings and Precautions
Laboratory Parameters: Elevated Liver Enzymes

Important Information

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

Recommendation in RA	Recommendation in PJIA	Recommendation in SJIA
• It is **NOT** recommended to initiate ACTEMRA treatment in patients with elevated transaminases ALT or AST greater than 1.5 times the upper limit of normal (ULN). • Monitor ALT and AST levels 4 to 8 weeks after start of therapy and every 3 months thereafter. • When clinically indicated, other liver function tests such as bilirubin should be considered.	• It is **NOT** recommended to initiate ACTEMRA treatment in patients with elevated transaminases ALT or AST greater than 1.5 times the upper limit of normal (ULN). • Monitor ALT and AST at the **time of the second infusion and thereafter every 4 to 8 weeks**. • When clinically indicated, other liver function tests such as bilirubin should be considered.	• It is **NOT** recommended to initiate ACTEMRA treatment in patients with elevated transaminases ALT or AST greater than 1.5 times the upper limit of normal (ULN). • Monitor ALT and AST at the **time of the second infusion and thereafter every 2 to 4 weeks**. • When clinically indicated, other liver function tests such as bilirubin should be considered.

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Dosage Modifications
Elevated Liver Enzymes

ALT or AST Value	Recommendation in RA	Recommendation in PJIA and SJIA
>1 to 3x ULN	• Dose modify concomitant DMARDs if appropriate. • For persistent increases in this range: - For patients receiving IV ACTEMRA, reduce dose to 4 mg per kg or hold ACTEMRA until ALT or AST have normalized. - For patients receiving SC ACTEMRA, reduce injection frequency to every other week or hold dosing until ALT or AST have normalized. Resume ACTEMRA at every other week and increase frequency to every week as clinically appropriate.	• Dose interruptions of ACTEMRA are recommended for liver enzyme abnormalities at levels similar to what is outlined for patients with RA. • If appropriate, dose modify or stop concomitant MTX and/or other medications. • Hold ACTEMRA dosing until the clinical situation has been evaluated.
>3 to 5x ULN (confirmed by repeating testing)	• Hold ACTEMRA dosing until less than 3x ULN and follow recommendation above for greater than 1 to 3x ULN. • For persistent increases greater than 3x ULN, discontinue ACTEMRA.	• Dose interruptions of ACTEMRA are recommended for liver enzyme abnormalities at levels similar to what is outlined for patients with RA. • If appropriate, dose modify or stop concomitant MTX and/or other medications. • Hold ACTEMRA dosing until the clinical situation has been evaluated.
>5x ULN	• Discontinue ACTEMRA	• The decision to discontinue ACTEMRA for a laboratory abnormality should be based on the medical assessment of the individual patient.

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Warnings and Precautions
Laboratory Parameters: Lipid Abnormalities

Important Information

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

Recommendation in RA, PJIA, and SJIA

- Assess lipid parameters approximately 4 to 8 weeks following initiation of ACTEMRA therapy, then at approximately 24 week intervals.
- Manage patients according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.
- Exercise caution when coadministering ACTEMRA with CYP3A4 substrate drugs where decrease in effectiveness is undesirable (e.g., lovastatin, atorvastatin, etc.).

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Warnings and Precautions
Immunosuppression/Malignancies

Important Information

- 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.

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Warnings and Precautions
Hypersensitivity Reactions, Including Anaphylaxis (1 of 2)

Important Information

- Hypersensitivity reactions, including anaphylaxis, have been reported in association with ACTEMRA and anaphylactic events with a fatal outcome have been reported with IV 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 of IV ACTEMRA, 0.2% (8 out of 4009) of patients in the IV all-exposure RA population, 0.7% (8 out of 1068) in the SC 6-month controlled RA trials, and in 0.7% (10 out of 1456) of patients in the SC all-exposure population.
- In the SJIA controlled trial with IV ACTEMRA, 1 out of 112 patients (0.9%) experienced hypersensitivity reactions that required treatment discontinuation.
- In the PJIA controlled trial with IV ACTEMRA 0 out of 188 patients (0%) in the ACTEMRA all-exposure population experienced hypersensitivity reactions that required treatment discontinuation.
  - Reactions that required treatment discontinuation included generalized erythema, rash, and uticaria.
  - Injection site reactions were categorized separately.
- In the postmarketing setting, events of hypersensitivity reactions, including anaphylaxis and death have occurred in patients treated with a range of doses of intravenous ACTEMRA, with or without concomitant arthritis therapies.
  - Events have occurred in patients who received premedication.
  - Hypersensitivity, including anaphylaxis events, have occurred both with and without previous hypersensitivity reactions and as early as the first infusion of ACTEMRA.

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Warnings and Precautions
Hypersensitivity Reactions, Including Anaphylaxis (2 of 2)

Recommendation in RA, PJIA, and SJIA

- 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.
- For ACTEMRA subcutaneous injection, advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction.

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Warnings and Precautions
Demyelinating Disorders

Important Information

- 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.

Recommendation in RA, PJIA, and SJIA

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

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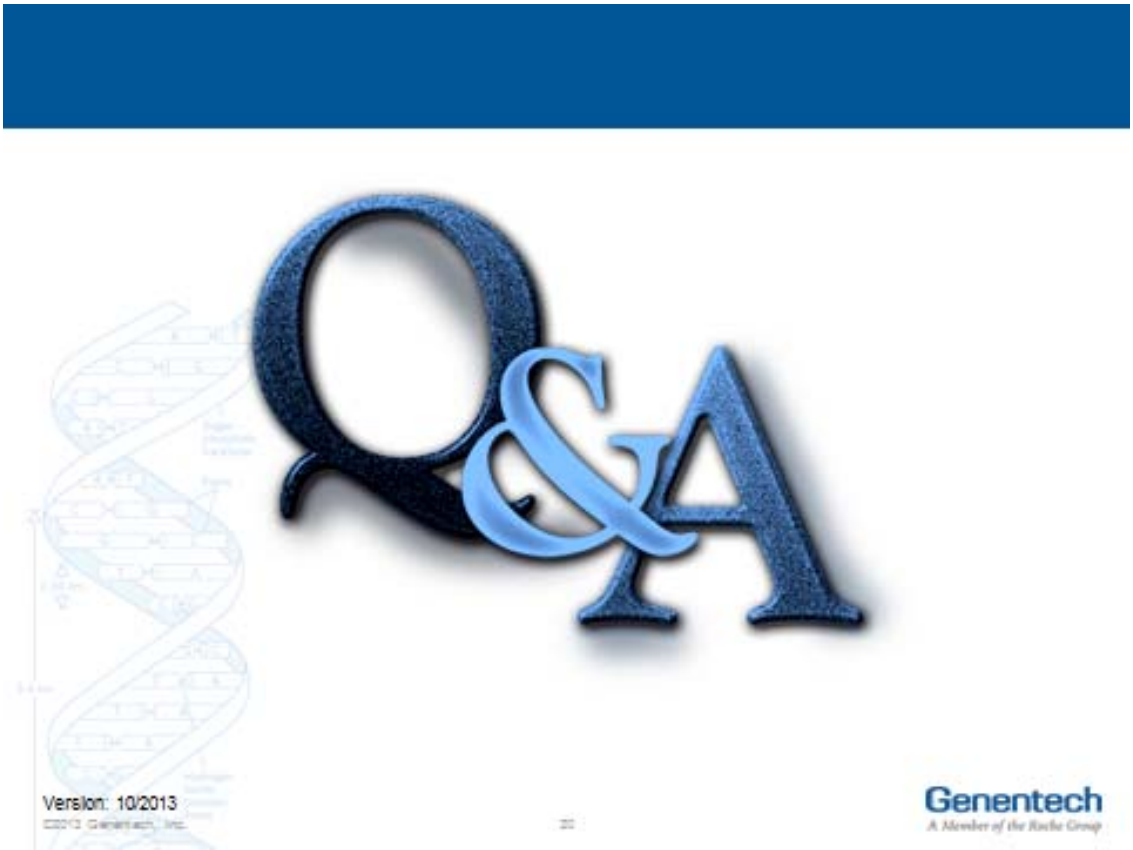
Q&A
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ATTACHMENT C: JOURNAL INFORMATION PIECE FOR EMERGENCY MEDICINE PHYSICIANS AND EMERGENCY MEDICAL SERVICES PROFESSIONALS

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 antagonist that has been approved by the Food and Drug Administration (FDA) for three 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 for intravenous (IV) or every other week or weekly for subcutaneous (SC) administration.

- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA dosing interval of every 4 weeks for IV administration.

- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA dosing interval of every 2 weeks for IV administration.

The safety and efficacy of ACTEMRA for conditions other than RA, PJIA 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 Prescribing Information for more information.

Hypersensitivity reactions, including anaphylaxis: Hypersensitivity reactions, including anaphylaxis, have been reported in association with ACTEMRA and anaphylactic events with a fatal outcome have been reported with intravenous infusion of ACTEMRA.

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

In the SJIA controlled trial with intravenous ACTEMRA, 1 out of 112 patients (0.9%) experienced hypersensitivity reaction that required treatment discontinuation. In the PJIA controlled trial with intravenous ACTEMRA, 0 out of 188 patients (0%) in the ACTEMRA all-exposure population experienced hypersensitivity reactions that required treatment discontinuation. Reactions that required treatment discontinuation included generalized erythema, rash and urticaria. Injection site reactions were categorized separately.

In the postmarketing setting, events of hypersensitivity reactions, including anaphylaxis and death have occurred in patients treated with a range of doses of intravenous ACTEMRA, with or without concomitant arthritis therapies. Events have occurred in patients who received premedication. Hypersensitivity, including anaphylaxis events, have occurred both with and without previous hypersensitivity reactions and as early as the first infusion of ACTEMRA.

ACTEMRA for intravenous use should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis. For ACTEMRA subcutaneous injection, advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, stop administration of ACTEMRA immediately and discontinue ACTEMRA permanently. Do not administer ACTEMRA to patients with known hypersensitivity to ACTEMRA.

Please see the 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 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 1-888-835-2555

- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for Prescribing Information and Medication Guide.

ATTACHMENT D: JOURNAL INFORMATION PIECE FOR GASTROENTEROLOGISTS AND HEPATOLOGISTS

Reference ID: 3394610

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 antagonist that has been approved by the Food and Drug Administration (FDA) for three 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 for intravenous (IV) or every other week or weekly for subcutaneous (SC) administration.

- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA dosing interval of every 4 weeks for IV administration.

- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA dosing interval of every 2 weeks for IV administration.

The safety and efficacy of ACTEMRA for conditions other than RA, PJIA 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. Monitor patients receiving ACTEMRA for elevated transaminase levels; dose modifications may be necessary. When clinically indicated, consider other liver function tests, such as bilirubin.

Please see the 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 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 1-888-835-2555
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for Prescribing Information and Medication Guide.

ATTACHMENT E: JOURNAL INFORMATION PIECE FOR INFECTIOUS DISEASE SPECIALISTS

Reference ID: 3394610

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

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist that has been approved by the Food and Drug Administration (FDA) for three 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 for intravenous (IV) or every other week or weekly for subcutaneous (SC) administration.
- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA dosing interval of every 4 weeks for IV administration.
- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA dosing interval of every 2 weeks for IV administration.

The safety and efficacy of ACTEMRA® for conditions other than RA, PJIA 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.

Avoid ACTEMRA during an active infection, including localized infections. If a serious infection develops, hold ACTEMRA 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 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 1-888-835-2555
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for Prescribing Information and Medication Guide.

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

Reference ID: 3394610

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

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist that has been approved by the Food and Drug Administration (FDA) for three 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 for intravenous (IV) or every other week or weekly for subcutaneous (SC) administration.

- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA dosing interval of every 4 weeks for IV administration.

- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA dosing interval of every 2 weeks for IV administration.

The safety and efficacy of ACTEMRA for conditions other than RA, PJIA 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, have been reported in association with ACTEMRA and anaphylactic events with a fatal outcome have been reported with intravenous 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 of intravenous ACTEMRA, 0.2% (8 out of 4009) of patients in the

intravenous all-exposure rheumatoid arthritis population, 0.7 % (8 out of 1068) in the SC 6-month controlled RA trials, and in 0.7% (10 out of 1465) of patients in the SC all-exposure population.

In the SJIA controlled trial with intravenous ACTEMRA, 1 out of 112 patients (0.9%) experienced hypersensitivity reaction that required treatment discontinuation. In the PJIA controlled trial with intravenous ACTEMRA, 0 out of 188 patients (0%) in the ACTEMRA all-exposure population experienced hypersensitivity reactions that required treatment discontinuation. Reactions that required treatment discontinuation included generalized erythema, rash and urticaria. Injection site reactions were categorized separately.

In the postmarketing setting, events of hypersensitivity reactions, including anaphylaxis and death have occurred in patients treated with a range of doses of intravenous ACTEMRA, with or without concomitant arthritis therapies. Events have occurred in patients who received premedication. Hypersensitivity, including anaphylaxis events, have occurred both with and without previous hypersensitivity reactions and as early as the first infusion of ACTEMRA.

ACTEMRA for intravenous use should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis. For ACTEMRA subcutaneous injection, advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, stop administration of ACTEMRA immediately and discontinue ACTEMRA permanently. Do not administer ACTEMRA to patients with known hypersensitivity to ACTEMRA.

Please see the 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. Monitor patients for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

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 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 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 1-888-835-2555
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for Prescribing Information and Medication Guide.

ATTACHMENT G: JOURNAL INFORMATION PIECE FOR NEUROLOGISTS

Reference ID: 3394610

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 antagonist that has been approved by the Food and Drug Administration (FDA) for three 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 for intravenous (IV) or every other week or weekly for subcutaneous (SC) administration.

- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA dosing interval of every 4 weeks for IV administration.

- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA dosing interval of every 2 weeks for IV administration.

The safety and efficacy of ACTEMRA for conditions other than RA, PJIA 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. Monitor patients for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

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 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 1-888-835-2555
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for Prescribing Information and Medication Guide.

ATTACHMENT H: JOURNAL INFORMATION PIECE FOR ONCOLOGISTS

Reference ID: 3394610

Important Safety Information for Oncologists
About Malignancy Risk With ACTEMRA®

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist that has been approved by the Food and Drug Administration (FDA) for three 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 for intravenous (IV) or every other week or weekly for subcutaneous (SC) administration.

- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA® dosing interval of every 4 weeks for IV administration.

- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks for IV administration.

The safety and efficacy of ACTEMRA for conditions other than RA, PJIA 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 a 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 1-888-835-2555
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for Prescribing Information and Medication Guide.

ATTACHMENT I: JOURNAL INFORMATION PIECE FOR RHEUMATOLOGISTS

Reference ID: 3394610

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

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist that has been approved by the Food and Drug Administration (FDA) for three 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 for intravenous (IV) or every other week or weekly for subcutaneous (SC) administration.

- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA dosing interval of every 4 weeks for IV administration.

- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA dosing interval of every 2 weeks for IV administration.

The safety and efficacy of ACTEMRA for conditions other than RA, PJIA 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.

Hypersensitivity Reactions, Including Anaphylaxis
Hypersensitivity reactions, including anaphylaxis, have been reported in association with ACTEMRA and anaphylactic events with a fatal outcome have been reported with intravenous infusion of ACTEMRA.

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 intravenous all-exposure rheumatoid arthritis population, 0.7 % (8 out of 1068) in the SC 6-month

controlled RA trials, and in 0.7% (10 out of 1465) of patients in the SC all-exposure population.

In the SJIA controlled trial with intravenous ACTEMRA, 1 out of 112 patients (0.9%) experienced hypersensitivity reaction that required treatment discontinuation. In the PJIA controlled trial with intravenous ACTEMRA, 0 out of 188 patients (0%) in the ACTEMRA all-exposure population experienced hypersensitivity reactions that required treatment discontinuation. Reactions that required treatment discontinuation included generalized erythema, rash and urticaria. Injection site reactions were categorized separately.

In the postmarketing setting, events of hypersensitivity reactions, including anaphylaxis and death have occurred in patients treated with a range of doses of intravenous ACTEMRA, with or without concomitant arthritis therapies. Events have occurred in patients who received premedication. Hypersensitivity, including anaphylaxis events, have occurred both with and without previous hypersensitivity reactions and as early as the first infusion of ACTEMRA.

ACTEMRA for intravenous use should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis. For ACTEMRA subcutaneous injection, advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, stop administration of ACTEMRA immediately and discontinue ACTEMRA permanently. Do not administer ACTEMRA to patients with known hypersensitivity to ACTEMRA.

Please see the 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. Monitor patients for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

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 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 1-888-835-2555
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at www.fda.gov/medwatch/report.htm

Please visit www.ACTEMRA.com for Prescribing Information and Medication Guide.

ATTACHMENT J: ACTEMRA REMS WEBSITE SCREENSHOT

ACTEMRA® tocilizumab

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

Prescriber Education Slide Deck

Healthcare Professional Letters

Dear Healthcare Professional Letter

Journal Information Pieces

Rheumatologist

Emergency Medicine Physicians

Gastroenterologists and Hepatologists

Infectious Disease Specialists

Internal Medicine Physicians

Neurologists

Oncologists

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.

/s/

SARAH K YIM
10/21/2013
Signing for Badrul Chowdhury, M.D., Ph.D.