

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125276

REMS

BLA 125276/0

ACTEMRA[®] (tocilizumab)
Human interleukin-6 receptor inhibitor

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the ACTEMRA[®] REMS are:

- To inform healthcare providers about the risks of 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[®].
- To inform patients about the serious risks associated with ACTEMRA[®] treatment.

1 II. REMS ELEMENTS

A. Medication Guide (FDCA Section 505-1 (e)(2))

In accordance with 21 CFR 208.24, a Medication Guide will be included in each ACTEMRA[®] vial package. This Medication Guide should be dispensed to each patient by the infusion site immediately prior to each ACTEMRA[®] administration.

The Medication Guide will also be available via sales representatives, the ACTEMRA[®] patient and professional websites, and a toll-free product information line (1-800-ACTEMRA).

Please see the appended Medication Guide (Attachment A).

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

Genentech, A Member of the Roche Group, will implement a communication plan to the following 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 B) will be distributed to rheumatologists, gastroenterologists, hepatologists, neurologists, oncologists, general practitioners, osteopaths, infectious disease specialists, family medicine specialists, internal medicine specialists, emergency medicine specialists, and infusion sites. This letter will be distributed within 60 days of product approval.

A Professional Label and a copy of the Medication Guide will also be distributed in this communication.

2. A Dear Pharmacist letter (see Attachment C) will be distributed to pharmacists. This letter will be distributed within 60 days of product approval.
3. Dissemination of information about the known and potential serious 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
 - 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* and *Neurology* for 3 years
 - c) For quarterly presentation as a printed information piece in the *Journal of Clinical Oncology* for 5 years

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

C. Timetable for Submission of Assessments

REMS assessments will be submitted to FDA at 18 months, 3 years, and 7 years after approval. 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: MEDICATION GUIDE

MEDICATION GUIDE
ACTEMRA® (AC-TEM-RA)
(tocilizumab)

Rx only

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

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

ACTEMRA can cause serious side effects including:

1. Serious Infections

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

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

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

Before starting ACTEMRA, tell your healthcare provider if you:

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

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

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

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

3. Changes in certain laboratory test results. Your healthcare provider should do blood tests before you start receiving ACTEMRA and every 4 to 8 weeks during treatment to check for the following side effects of ACTEMRA:

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

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

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

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

4. Cancer.

ACTEMRA may decrease the activity of your immune system. Medicines that affect the immune system may increase your risk of certain cancers. Tell your healthcare provider if you have ever had any type of cancer.

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

What is ACTEMRA?

ACTEMRA is a prescription medicine called an Interleukin-6 (IL-6) receptor inhibitor. ACTEMRA is used to treat adults with moderately to severely active rheumatoid arthritis (RA) after at least one other medicine called a Tumor Necrosis Factor (TNF) antagonist has been used and did not work well.

It is not known if ACTEMRA is safe and effective in children.

What should I tell my healthcare provider before receiving ACTEMRA?

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

- have an infection. See “What is the most important information I should know about ACTEMRA?”
- have liver problems
- have any stomach-area (abdominal) pain or been diagnosed with diverticulitis or ulcers in your stomach or intestines
- have or had a condition that affects your nervous system, such as multiple sclerosis
- have recently received or are scheduled to receive a vaccine. People who take ACTEMRA should not receive live vaccines. People taking ACTEMRA can receive non-live vaccines
- plan to have surgery or a medical procedure

- have any other medical conditions
- plan to become pregnant or are pregnant. It is not known if ACTEMRA will harm your unborn baby.

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

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

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

Especially tell your healthcare provider if you take:

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

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

How will I receive ACTEMRA?

- You will receive ACTEMRA from a healthcare provider through a needle placed in a vein in your arm (IV or intravenous infusion). The infusion will take about 1 hour to give you the full dose of medicine.
- You will receive a dose of ACTEMRA about every 4 weeks.
- If you miss a scheduled dose of ACTEMRA, ask your healthcare provider when to schedule your next infusion.
- While taking ACTEMRA, you may continue to use other medicines that help treat your rheumatoid arthritis such as methotrexate, non-steroidal anti-inflammatory drugs (NSAIDs) and prescription steroids, as instructed by your healthcare provider.
- Keep all of your follow-up appointments and get your blood tests as ordered by your healthcare provider.

What are the possible side effects with ACTEMRA?

ACTEMRA can cause serious side effects, including:

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

- skin rash
- **Nervous system problems.** Multiple Sclerosis has been diagnosed rarely in people who take ACTEMRA. It is not known what effect ACTEMRA may have on some nervous system disorders.
- **Allergic Reactions.** Serious allergic reactions can happen with ACTEMRA. These reactions may not happen with your first infusion, and may happen with future infusions of ACTEMRA. Tell your healthcare provider right away if you have any of the following signs of a serious allergic reaction:
 - shortness of breath or trouble breathing
 - skin rash
 - swelling of the lips, tongue, or face
 - chest pain
 - feeling dizzy or faint

Common side effects of ACTEMRA include:

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

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

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

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

General information about ACTEMRA

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

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

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

What are the ingredients in ACTEMRA?

Active ingredient: tocilizumab

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

Genentech, Inc.

A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
US License No.1048

MG Issued: Month Year

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

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ATTACHMENT B: DEAR HEALTHCARE PROVIDER LETTER

January 2010

**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), a new interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies.

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, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, demyelinating disorders and malignancies.

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 III clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess. 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.

- During the six-month Phase III clinical trials, the overall rate of GI perforations was 0.26 events per 100 patient-years with ACTEMRA therapy versus no events for control.
- Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate.

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. 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 III 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. Total cholesterol and low-density lipoproteins should be measured 4 to 8 weeks after the first infusion and every 6 months thereafter. 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

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 and Medication Guide for a complete description of these risks.

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 before each infusion. This Medication Guide contains information that can be used to facilitate discussions about the known and potential risks of therapy. A copy is enclosed.

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.ACTEMRA.com

Sincerely,

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

Enclosure

ATTACHMENT C: DEAR PHARMACIST LETTER



January 2010

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

Dear Pharmacist:

The purpose of this letter is to inform you of important safety information for ACTEMRA® (tocilizumab), a new interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies.

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, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, demyelinating disorders and malignancies.

MEDICATION GUIDE

The FDA requires that a copy of the enclosed ACTEMRA Medication Guide be distributed to each patient who receives ACTEMRA. An ACTEMRA Medication Guide will be packaged with every vial of ACTEMRA. You should ensure that each dispensed vial of ACTEMRA includes a Medication Guide.

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

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 III clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula and abscess. 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.
- During the six-month controlled clinical trials, the overall rate of GI perforations was 0.26 events per 100 patient-years with ACTEMRA therapy versus no events for control.
- Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids or methotrexate.

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. 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 III 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. Total cholesterol and low-density lipoproteins should be measured 4 to 8 weeks after the first infusion and every 6 months thereafter. 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. 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.

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

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

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

Sincerely,

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

Enclosure

**ATTACHMENT D: 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 a new interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies. **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 III 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 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.

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

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

**ATTACHMENT E: 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 a new interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies. **Gastroenterologists** and **hepatologists** should be aware of important safety information regarding ACTEMRA.

Gastrointestinal perforations: Gastrointestinal (GI) perforation has been reported in Phase III 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 in Phase III 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

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

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

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

ACTEMRA® (tocilizumab) is a new interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies. **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

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

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

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

ACTEMRA® (tocilizumab) is a new interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies. 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 III 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. 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, lipids, neutrophils and platelets should be monitored, as abnormalities in these parameters were associated with ACTEMRA treatment in Phase III 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

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

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

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

ACTEMRA® (tocilizumab) is a new interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies. **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. 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 RA 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

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

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

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

ACTEMRA® (tocilizumab) is a new interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies. **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

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

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

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

ACTEMRA® (tocilizumab) is a new interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies. 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) perforations have been reported in Phase III 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. 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, lipids, neutrophils and platelets should be monitored, as abnormalities in these parameters were associated with ACTEMRA treatment in Phase III 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)
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