

May 2013

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

Dear Healthcare Provider:

The purpose of this letter is to inform you of important safety information for ACTEMRA® (tocilizumab), an interleukin-6 (IL-6) receptor inhibitor that has been approved by the Food and Drug Administration (FDA) for 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.
- Children 2 years of age and older with active *Polyarticular Juvenile Idiopathic Arthritis (PJIA)* with a recommended ACTEMRA® dosing interval of every 4 weeks.
- Children 2 years of age and older with active *Systemic Juvenile Idiopathic Arthritis (SJIA)* with a recommended ACTEMRA® dosing interval of every 2 weeks.

The safety and efficacy of ACTEMRA® for conditions other than RA, 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.
- ACTEMRA should not be administered during an active infection, including localized infections. If a serious infection develops, ACTEMRA should be interrupted until the infection is controlled.

- Prior to initiating ACTEMRA, a test for latent TB should be performed. If the test is positive, treatment for TB should be started prior to starting ACTEMRA. All patients should be monitored for active TB during treatment, even if the initial latent TB test is negative.

### ***Gastrointestinal Perforations***

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

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

- Hypersensitivity reactions, including anaphylaxis and death, have been reported in association with infusion of ACTEMRA.
- Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials, and in 0.2% (8 out of 4009) of patients in the all-exposure rheumatoid arthritis population; and in the SJIA controlled trial, 1 out of 112 patients (0.9%).
- In the postmarketing setting, events of clinically significant hypersensitivity, and anaphylaxis, including events with a fatal outcome, have occurred in patients treated with a range of doses of ACTEMRA, with or without concomitant arthritis therapies. Events have occurred in patients who received premedication. Clinically significant hypersensitivity and anaphylaxis events have occurred both with and without previous hypersensitivity reactions and as early as the first infusion of ACTEMRA.
- ACTEMRA should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis. If anaphylaxis or other clinically significant hypersensitivity reaction occurs, administration of ACTEMRA should be stopped immediately and ACTEMRA should be permanently discontinued. Do not administer ACTEMRA to patients with known hypersensitivity to ACTEMRA.

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

- The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies of adults with RA. Patients should be closely monitored for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

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

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

## **IMPORTANT INFORMATION ON LABORATORY ABNORMALITIES**

Hepatic transaminases, lipids, neutrophils and platelets should be monitored, as abnormalities in these parameters were associated with ACTEMRA treatment in Phase 3 clinical trials. Prior to initiating treatment

with ACTEMRA, it is recommended that appropriate baseline laboratory parameters be measured. While on ACTEMRA, liver aminotransferases (ALT, AST), neutrophil counts, and platelet counts should be measured every 4 to 8 weeks for RA and PJIA and at the time of the second infusion and, thereafter, every 2 to 4 weeks for SJIA. Total cholesterol and low-density lipoproteins should be measured 4 to 8 weeks after the first infusion and every 6 months thereafter for RA, PJIA and SJIA. Dosage modifications may be required if laboratory abnormalities occur. Please see the accompanying full Prescribing Information for more information.

## REPORTING ADVERSE EVENTS

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

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

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

## FULL PRESCRIBING INFORMATION AND MEDICATION GUIDE

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

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

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

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

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

Sincerely,



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Enclosure