Genentech
A Member of the Roche Group

October 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 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, 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.

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
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Genentech, Inc.

Enclosure

Version: October 2013