

**IMPORTANT
DRUG
WARNING**

June 2019

Subject: Serious Risk with Use of ACTEMRA® (tocilizumab):

- **Risk of Hepatotoxicity**

Dear Health Care Provider:

The purpose of this letter is to inform you of important safety information for ACTEMRA® (tocilizumab), a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass. It is approved for 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), adult patients with giant cell arteritis (GCA), patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (pJIA), patients 2 years of age and older with active systemic juvenile idiopathic arthritis (sJIA), and adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS).

Serious Risk with Use of ACTEMRA®

Risk of Hepatotoxicity:

- Tocilizumab is known to cause transient or intermittent mild to moderate elevation of hepatic transaminases and in particular with increased frequency when used in combination with potentially hepatotoxic drugs (e.g., methotrexate).
- Based on comprehensive cumulative analysis of all available global clinical and postmarketing safety data, eight cases of tocilizumab-related serious hepatic injury were identified, including reports of acute liver failure/liver transplant, hepatitis, and jaundice. These events occurred between 2 weeks to more than 5 years after initiation of tocilizumab, with median latency of 98 days.
- The frequency of the observed serious hepatotoxicity events is considered rare, and the benefit-risk profile of tocilizumab in the approved indications remains favorable.

Prescriber Action

- The currently approved prescribing information does not recommend treatment with tocilizumab in patients with elevated alanine aminotransferase (ALT) or aspartate

aminotransferase (AST) above 5x upper limit of normal (ULN). It is not recommended to initiate ACTEMRA® treatment in patients with elevated transaminases ALT or AST greater than 1.5x ULN.

- To ensure adequate safety monitoring given this newly identified important risk, in patients with RA and GCA, ALT and AST should now be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For pJIA and sJIA patients, monitor ALT and AST at the time of the second administration and thereafter every 4 to 8 weeks for pJIA and every 2 to 4 weeks for sJIA.
- Patients should be informed about the risk of hepatic injury and the need for periodic monitoring. Patients presenting with signs or symptoms suggestive of hepatic dysfunction should be evaluated for liver injury.
- Recommended dose modifications (reduction, interruption, or discontinuation) of tocilizumab due to liver enzyme abnormalities remain unchanged; refer to the guidance in the enclosed full prescribing information.
- Please note, the above mentioned actions do not apply to the indication for treatment of cytokine release syndrome (CRS). Patients with severe or life-threatening CRS frequently have cytopenias or elevated ALT or AST due to the lymphodepleting chemotherapy or the CRS. The decision to administer tocilizumab should take into account the potential benefit of treating the CRS versus the risks of short-term treatment with tocilizumab.

Reporting Adverse Events

Health Care Providers should report any adverse events suspected to be associated with the use of ACTEMRA® to Genentech at 1-888-835-2555.

Alternatively, this information may be reported to the FDA's MedWatch reporting system by phone (1-800-FDA-1088) or online (www.fda.gov/medwatch).

Company Contact Point

Should you have any questions about the information in this letter or the safe and effective use of ACTEMRA®, please feel free to contact the Genentech Medical Information/Communications Department at 1-800-821-8590.

This letter is not intended as a complete description of the benefits and risks related to the use of ACTEMRA®. Please refer to the enclosed full prescribing information.

Sincerely,



Susan Begelman, M.D., F.A.C.C.
Vice President and Interim Head of U.S. Medical Affairs