7 May 2019

IMPORTANT SAFETY UPDATE – ACTEMRA® (tocilizumab)

A new important identified risk: Hepatoxicity

Dear Healthcare Provider,

Roche Products (New Zealand) Limited ("Roche") wishes to inform you of important new safety information for Actemra.

Summary

- Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, in some cases requiring liver transplant, have been observed with the administration of Actemra/ (tocilizumab). The frequency of serious hepatotoxicity is considered rare.
- 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). Caution should continue to be exercised when considering initiation of tocilizumab treatment in patients with ALT or AST above 1.5x ULN.
- In patients with Rheumatoid Arthritis (RA), Giant Cell Arteritis (GCA), Polyarticular Juvenile Idiopathic Arthritis (pJIA) and Systemic Juvenile Idiopathic Arthritis (sJIA), 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.
- Recommended dose modifications (reduction, interruption or discontinuation) of tocilizumab due to liver enzyme abnormalities remain unchanged, refer to the guidance in the approved label.

Background on the safety concern

Tocilizumab is indicated for treatment of:

- Rheumatoid Arthritis (RA) [IV and SC formulations]

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- Giant Cell Arteritis (GCA) in adult patients [SC formulation only]
- Polyarticular Juvenile Idiopathic Arthritis (pJIA) [IV formulation only] in patients 2 years of age and older.
- Systemic Juvenile Idiopathic Arthritis (sJIA) [IV formulation only] in patients 2 years of age and older.

PHARMAC also funds tocilizumab off-label for:

- Castleman's disease
- Treatment of Cytokine Release Syndrome (CRS) in two clinical trials

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). A cumulative, comprehensive assessment of serious hepatic injury including hepatic failure reported with tocilizumab was performed across all available clinical and post marketing data sources including data from FDA Adverse Event Reporting System (FAERS) and Eudravigilance (EV) databases and from the literature.

The Marketing Authorization Holder (MAH) has identified eight cases of tocilizumab related moderate to severe drug-induced liver injury including acute liver failure, hepatitis and jaundice. These events occurred between 2 weeks to more than 5 years after initiation of tocilizumab with median latency of 98 days. In these eight cases, two cases of acute liver failure required liver transplantation. In the context of total world-wide tocilizumab exposure of approximately 1,066,849 patients (882,370.3PY) up to 10th April 2018, these events are considered rare and the benefit-risk profile of tocilizumab in the approved indications remains favorable.

To ensure adequate safety monitoring given this newly identified important risk, in RA, GCA, pJIA and sJIA patients, 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.

Roche is working closely with health authorities to update the product label to reflect this identified risk of hepatotoxicity and to extend the frequency of monitoring of hepatic transaminases to sJIA and pJIA indications. Healthcare Professionals should follow the guidance including dose modification and tocilizumab discontinuation as per the approved label.

Roche will be working with Medsafe to update the Data Sheet to include this new risk.

Before prescribing, please review the full Actemra Data Sheet available at www.medsafe.govt.nz.

If you have any questions or require additional information regarding the use of Actemra please contact Roche Medical Information on 0800 276 243 or email auckland.medinfonz@roche.com.

Reporting Adverse Events

Roche will continue to monitor the safety of Actemra through established reporting mechanisms and notify regulatory authorities of any serious adverse events for evaluation.

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Please report any suspected adverse events via email to Roche Drug Safety at nz.drugsafety@roche.com. Alternatively, this information may be reported to the Centre for Adverse Reactions Monitoring (CARM) in Dunedin by telephone on (03) 479 7247, online at https://nzphvc.otago.ac.nz/reporting, by email to nzphvc@otago.ac.nz or by fax on (03) 479 7150.

Yours sincerely

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