

27th June 2019

RoActemra® (tocilizumab): Rare risk of serious hepatic injury including acute liver failure requiring transplantation

Dear Healthcare professional,

F. Hoffmann-La Roche in agreement with the European Medicines Agency and the Health Products Regulatory Authority (HPRA) would like to inform you of the following:

Summary

- Serious cases of drug-induced liver injury, including acute liver failure, hepatitis and jaundice, in some cases requiring liver transplantation, have been observed in patients treated with tocilizumab. The frequency of serious hepatotoxicity is considered rare.
- Advise patients to immediately seek medical help if they experience signs and symptoms of hepatic injury.
- ALT and AST should be monitored every 4 to 8 weeks for the first 6 months of treatment, followed by every 12 weeks thereafter in patients with rheumatological indications.
- Caution should be exercised when considering treatment initiation in patients with ALT or AST $>1.5\times$ ULN. Treatment is not recommended in patients with ALT or AST $>5\times$ ULN.
- If liver enzyme abnormalities are identified, dose modifications (reduction, interruption or discontinuation) of tocilizumab may be necessary. The recommended dose modifications remain unchanged (see guidance in the approved product information).

Background on the safety concern

Tocilizumab is indicated for treatment of:

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

Tocilizumab is known to cause transient or intermittent mild to moderate elevation of hepatic transaminases, with increased frequency when used in combination with potentially hepatotoxic drugs (e.g. methotrexate).

A cumulative assessment of serious hepatic injury including hepatic failure reported with tocilizumab identified 8 cases of tocilizumab-related drug-induced liver injury including

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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. Two cases of acute liver failure required liver transplantation.

Based on the data from clinical trials these events of serious liver injury are considered to be rare and the benefit-risk profile of tocilizumab in the approved indications remains favorable

In RA, GCA, pJIA and sJIA patients, ALT and AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter.

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.

Recommended dose modifications (reduction, interruption or discontinuation) of tocilizumab due to liver enzyme abnormalities remain unchanged, refer to the guidance in the approved product information.

Please note, these updates do not apply to the indication for treatment of cytokine release syndrome (CRS).

Call for reporting

Health care professionals should report any adverse events suspected to be associated with the use of RoActemra® (tocilizumab) to: the Drug Surveillance Centre in Roche Products (Ireland) Limited by mail, telephone (01-4690700), fax (01-4690793) or email (Ireland.drug_surveillance_centre@roche.com).

Suspected adverse reactions should be reported to the HPRA using a Yellow Card obtained either from the HPRA, or electronically via the website at www.hpra.ie. Adverse reactions can also be reported to the HPRA by calling (01) 676 4971.

Company contact point

Should you have any questions regarding the use of RoActemra® (tocilizumab), please feel free to contact Medical Information at Roche Products (Ireland) Limited by telephone (01 4690700), fax (01 4690791) or email (Ireland.druginfo@roche.com).

Yours sincerely,



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