



Date: 27 June 2019

Ref: RCUKACTE01882

Direct Healthcare Professional Communication

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

Dear Healthcare Professional,

F. Hoffmann-La Roche Ltd in agreement with the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency (MHRA) 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.
- Caution should be exercised when considering treatment initiation in patients with ALT or AST >1.5x ULN. Treatment is not recommended in patients with ALT or AST >5x 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 Summary of Product Characteristics).

Background on the safety concern

Tocilizumab is indicated for treatment of:

- Rheumatoid Arthritis (RA),
- Giant Cell Arteritis (GCA) in adult patients [SC formulation only],

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- 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 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 favourable.

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. This represents a change in the monitoring recommendation for those patients treated for sJIA and pJIA, which has been harmonised with the monitoring guidance for RA and GCA patients.

The Summary of Product Characteristics (SPC) does not currently reflect this change, but this advice should be up taken immediately. SPC updates will be made in due course.

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 Summary of Product Characteristics.

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

Call for reporting

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme.

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Please report:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason.

It is easiest and quickest to report ADRs online via the Yellow Cards website - <https://yellowcard.mhra.gov.uk/> or search for MHRA Yellow Card in the Google Play or Apple App Store.

Alternatively, prepaid Yellow Cards for reporting are available:

- by writing to FREEPOST YELLOW CARD (no other address details necessary)
- by emailing yellowcard@mhra.gov.uk
- at the back of the British National Formulary (BNF)
- by telephoning the free phone line for the Yellow Card Scheme at: 0800-731-6789
- or by downloading and printing a form available at <https://yellowcard.mhra.gov.uk/downloadable-information/reporting-forms/>

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.uk_dsc@roche.com or calling +44 (0)1707 367554.

As RoActemra is a biological medicine, healthcare professionals should report adverse reactions by brand name and batch number.

Company contact point

For further information or any questions please contact Roche Medical Information by phone on +44(0)800 328 1629 or via e-mail medinfo.uk@roche.com

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Annexes

Prescribing Information for RoActemra (tocilizumab) is available either via The European Medicines Agency website at <http://www.ema.europa.eu/ema/>, via the MHRA website at <http://www.mhra.gov.uk/spc-pil/> or via the Electronic Medicines Compendium at <http://www.medicines.org.uk/emc> and will be updated.

Yours faithfully,

A handwritten signature in black ink, appearing to read "Rav Seeruthun".

Dr Rav Seeruthun MBBS BSc MRCGP MFPM MBA
UK Medical Director