Important Safety Information on ACTEMRA® (tocilizumab) – Risk of Hepatotoxicity

2019/05/21

Audience
Healthcare professionals including adult and pediatric rheumatologists, hepatologists, gastroenterologists, as well as internists, pediatricians, prescribing physicians, pharmacists, emergency room staff, and nurses in rheumatology clinics, hospital wards and patient care centres where ACTEMRA is administered.

Key messages

- **Serious drug-induced liver injury (DILI), in some cases resulting in acute liver failure requiring a transplant, has been reported in patients treated with ACTEMRA.**
- **Healthcare professionals are advised to:**
  - **not recommend ACTEMRA in patients with active hepatic disease or hepatic impairment;**
  - **not initiate treatment with ACTEMRA in patients with elevated blood liver enzyme levels above 3 times the upper limit of normal (ULN);**
  - **discontinue treatment with ACTEMRA in patients with elevated blood liver enzyme levels above 5 times the ULN;**
  - **exercise caution when considering starting ACTEMRA treatment in patients with liver enzyme levels above 1.5 times the ULN;**
  - **monitor liver function tests (LFTs) in patients with rheumatoid arthritis and giant cell arteritis every 4 to 8 weeks for the first 6 months of treatment, followed by every 12 weeks thereafter;**
  - **monitor LFTs in patients with polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis before treatment begins, at the time of the second ACTEMRA treatment, and every 2 to 4 weeks thereafter;**
  - **refer to the approved Canadian Product Monograph for guidance on the recommended dose adjustments (reduction, interruption or discontinuation) in patients with liver enzyme elevations; and**
  - **advise patients to contact a healthcare professional if they experience signs of liver injury such as loss of appetite, nausea and vomiting, fatigue, itching, dark urine, yellowing of skin and eyes, abdominal swelling and/or pain in the upper-right abdomen.**

- **Health Canada is working with the manufacturer to include this new safety information in the Canadian Product Monograph.**

What is the issue?
Serious cases of drug-induced liver injuries (DILI) have been reported in patients treated with ACTEMRA, including cases of acute liver failure requiring a transplant. There have been cases of serious liver injury reported from Canada.

Products affected
ACTEMRA (tocilizumab): 20 mg/mL concentrate solution for intravenous infusion (IV) in 4 mL, 10 mL, and 20 mL vials, and 162 mg/0.9 mL solution for subcutaneous (SC) injection.

Background information
ACTEMRA has market authorization in Canada for use in the following indications:

1. Rheumatoid Arthritis [IV or SC formulations]
ACTEMRA is indicated for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis.

ACTEMRA (IV only) in combination with methotrexate (MTX) has been shown to reduce the rate of progression of radiographic joint damage at week 52.

ACTEMRA is to be given in combination with MTX or other disease-modifying antirheumatic drugs (DMARDs). However, in cases of intolerance to MTX or where treatment with MTX is not appropriate, ACTEMRA may also be given as monotherapy.

2. Giant Cell Arteritis [SC formulation only]
ACTEMRA is indicated for the treatment of giant cell arteritis in adult patients.

3. Polyarticular Juvenile Idiopathic Arthritis [IV or SC formulations]
ACTEMRA is indicated for the treatment of signs and symptoms of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older who have responded inadequately to previous therapy with DMARDs.

4. Systemic Juvenile Idiopathic Arthritis [IV formulation only]
ACTEMRA is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older, who have responded inadequately to previous therapy with one or more non-steroidal anti-inflammatory drugs and systemic corticosteroids.

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

Following Health Canada's request, the Market Authorization Holder performed a cumulative, comprehensive assessment of serious hepatic injury including hepatic failure reported with ACTEMRA across all available clinical and post-marketing data sources, including data from the Food and Drug Administration Adverse Event Reporting System (FAERS) and Eudravigilance (EV) databases and from the literature. Eight cases of ACTEMRA-related moderate to severe DILI were identified. These events occurred between 2 weeks to more than 5 years after initiation of tocilizumab with median latency of 98 days. Two of these 8 cases required liver transplantation. The total world-wide ACTEMRA exposure is estimated to be 1,066,849 patients (corresponding to 882,370.3 Patient Years) up to April 10, 2018.

Information for consumers

ACTEMRA is a prescription medicine used to treat:

- adults with moderate to severe rheumatoid arthritis;
- adults with giant cell arteritis, an inflammation in the arteries, especially the ones in the temples; and
- children older than 2 years with certain types of arthritis.

In some patients, ACTEMRA has been associated with drug-induced liver injuries, which can be serious, life-threatening or even fatal.

Before taking ACTEMRA, patients or their caregivers should talk to their healthcare professional if they have, or have had, liver problems. Before and/or during treatment, patients should have blood tests done to check their liver function.

If patients experience signs of liver injury such as loss of appetite, nausea and vomiting, fatigue, itching, dark urine, yellowing of skin and eyes, abdominal swelling, and/or pain in the upper-right abdomen, they or their caregivers should speak with their healthcare professional. Patients receiving ACTEMRA should also inform their healthcare professional if they experience any adverse effects.

Patients or their caregivers should contact their healthcare professional to obtain further information on this new safety information.

Information for healthcare professionals

Healthcare professionals are advised to:

- not recommend ACTEMRA in patients with active hepatic disease or hepatic impairment;
- not initiate treatment with ACTEMRA in patients with elevated blood liver enzyme levels (alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase) above 3 times the ULN;
- discontinue treatment with ACTEMRA in patients with elevated blood liver enzyme levels above 5 times the ULN;
- exercise caution when considering initiation of ACTEMRA treatment in patients with liver enzyme levels above 1.5 times the ULN;

- monitor liver function tests (LFTs) in patients with rheumatoid arthritis and giant cell arteritis every 4 to 8 weeks for the first 6 months of treatment, followed by every 12 weeks thereafter;
- monitor LFTs in patients with polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis before starting treatment, at the time of the second ACTEMRA treatment, and every 2 to 4 weeks thereafter; and
- consult the approved Canadian Product Monograph for guidance on the recommended dose modifications in patients with elevated LFTs.

Action taken by Health Canada

Health Canada is currently assessing the risk of ACTEMRA-associated liver injury and is working with Hoffmann-La Roche Limited to update the Canadian Product Monograph to include this safety information. Health Canada is communicating this important safety information to healthcare professionals and Canadians via the Recalls and Safety Alerts Database on the Healthy Canadians Web Site (https://healthycanadians.gc.ca/recall-alert-rappel-avis/index-eng.php). This communication will be further distributed through the MedEffect™ e-Notice email notification systemas well as social media channels including LinkedIn and Twitter.

Report health or safety concerns

Health Canada's ability to monitor the safety of marketed health products depends on healthcare providers and consumers reporting adverse reactions and medical device incidents. Any case of hepatotoxicity or other serious or unexpected adverse reactions in patients receiving ACTEMRA should be reported to Hoffmann-La Roche Limited or Health Canada.

Hoffmann-La Roche Limited
Drug Safety Department
7070 Mississauga Road
Mississauga, Ontario, L5N 5M8
Toll free: 1-888-762-4388
Fax: 905-542-5864
E-mail: mississauga.drug_safety@roche.com

To correct your mailing address or fax number, contact Hoffmann-La Roche Limited.

You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

- Calling toll-free at 1-866-234-2345; or
- Visiting MedEffect Canada's Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax.

For other health product inquiries related to this communication, please contact Health Canada at:
Marketed Health Products Directorate
E-mail: mhpd-dpsc@canada.ca
Telephone: 613-954-6522
Fax: 613-952-7738

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