Date: 02/09/2015

Direct Healthcare Professional Communication (DHPC).

Dear Healthcare Provider,

Hoffmann-La Roche Ltd. Saudi Arabia (hereafter referred to as Roche) would like to inform you about recommendations concerning the treatment of patients with Actemra® (Tocilizumab).

Summary:
This communication contains reminders about the Warning and Precautions of Actemra and is part of the Risk Minimization Activities to increase awareness about the Actemra safety profile.

Important Actemra safety information

- **Infections:**

Serious and sometimes fatal infections have been reported in patient's receiving immunosuppressive agents including Tocilizumab.

Actemra® should not be administered to patients with active infection. Patients with recurrent infections or with underlying diseases predisposing to infection (e.g. diverticulitis or diabetes) should be treated with caution.

Vigilance for the timely detection of serious infection is recommended for patients receiving biological treatments for RA as signs and symptoms of acute inflammation may be lessened, associated with suppression of the acute phase reaction. The effects of Actemra® on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection according to local Summery Product **Characteristics** SPC.

- **Viral reactivation:**

Viral reactivation (e.g. hepatitis B virus) has been observed with the use of immunosuppressant in rheumatoid arthritis. No case of Hepatitis B reactivation was observed in trials; however, patients who screened positive for hepatitis were excluded.

- **Preventive vaccinations:**

Avoid use of live vaccines concurrently with Actemra® as clinical safety has not been established.

- **Complications of diverticulitis:**

Cases of diverticular perforation have been reported in adults as a complication of diverticulitis. Actemra® should be used with caution in patients who may be at increased risk for gastrointestinal perforation. Patients presenting with new onset

abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

- **Hypersensitivity reactions:**

Serious hypersensitivity reactions, including anaphylaxis have been reported in association with Tocilizumab. In the post marketing setting, events of serious hypersensitivity and anaphylaxis, including reports of fatal anaphylaxis, have occurred in patients treated with a range of doses of Tocilizumab, with or without concomitant arthritis therapies, premedication, and / or a previous hypersensitivity reaction. These events have occurred as early as the first infusion of Tocilizumab. Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during infusion with Tocilizumab. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of Tocilizumab should be stopped immediately and Tocilizumab should be permanently discontinued

Anaphylactic reactions may present in particular with circulatory symptoms, bronchial obstruction, angioedema (with possible airway involvement) and abdominal or cutaneous symptoms (urticaria, erythema, pruritus). Before receiving Actemra®, patients should be asked whether they have experienced such symptoms or other adverse reactions to previous infusions and, if so, how they tolerated them. It should also be ensured that appropriate facilities and staff are available for emergency treatment of anaphylactic reactions. Patients must be closely monitored during and after the infusion. In the event of an anaphylactic or other serious hypersensitivity reaction, Tocilizumab administration must be immediately and permanently stopped, and appropriate treatment initiated (positioning, oxygen, volume replacement plus intramuscular adrenaline [epinephrine], generally in 0.3 mg doses, followed by further drugs such as antihistamines and glucocorticosteroids). Actemra® must be permanently discontinued in these patients.

- **Demyelinating disorders:**

Physicians should be vigilant for symptoms potentially indicative of new-onset demyelinating disorders. The potential for CNS demyelination with Actemra® is currently unknown.

- **Malignancy:**

Patients with rheumatoid arthritis are at increased risk of malignancy. Actemra® is an immunosuppressant and treatment with immunosuppressant may increase the risk of malignancy. Clinical data is insufficient to estimate the possible incidence of malignancies after Actemra® administration.

- **Laboratory abnormalities:**

Active hepatic disease and hepatic impairment: An increase in transaminases may occur during Actemra® therapy, in particular during co-administration with MTX. For this reason, caution is essential when administering Actemra® to patients with active

hepatic disease or hepatic impairment. In the clinical trials, a mild to moderate, transient and sometimes recurrent increase was observed in transaminases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) during Actemra® therapy, without resulting in chronic hepatic impairment. This increase was more often observed when potentially hepatotoxic drugs (for example, MTX) were used in combination with Actemra®. In patients with elevated transaminases (ALT or AST >1.5 × upper limit of normal [ULN]), Actemra® therapy must be initiated with caution. Actemra® should not be administered to patients with ALT or AST >5 × ULN. In adult patients, transaminase levels should be checked 4–8 weeks after starting treatment, then as often as considered necessary by the attending physician.

If ALT/AST levels >3–5 × ULN are confirmed on repeat testing, Actemra® therapy should be interrupted. Actemra® treatment can be reintroduced at a dosage of 4 or 8 mg/kg BW once the patient's transaminases return to levels <3 × ULN.

Effect on complete blood count: cases of decreased neutrophil and platelet counts have been observed on treatment with Actemra® combined with standard DMARDs. In patients with a low neutrophil or platelet count (i.e. absolute counts of <2 × 109/l and <100 × 103/µl, respectively), caution must be observed when initiating Actemra® therapy. Treatment is not recommended in patients with absolute counts of <0.5 × 109/l neutrophils or <50 × 103/µl platelets. Neutrophil and platelet counts should be checked 4–8 weeks after starting treatment, then as often as considered necessary by the attending physician.

Lipid parameters: Elevations in lipid parameters such as total cholesterol, triglycerides and/or low-density lipoprotein (LDL) have been observed. , lipid parameters should be measured 4 to 8 weeks after the start of Actemra therapy.

*Please refer to the Saudi SPC for further safety information, including list of all warning and precautions and Adverse Events section

Call for reporting:
Health care professionals should report any serious adverse events suspected to be associated with the use of Actemra® according to national reporting requirements.

Saudi Food and Drug Authority (SFDA)

Toll free phone: 8002490000

Fax: +966-11-205-7662

E-mail: npc.drug@sfda.gov.sa

Or by online: https://ade.sfda.gov.sa/

Company contact point:
Should you have any questions or require additional information regarding the use of please feel free to contact.

Local Safety Responsible
Hoffmann La-Roche
Najoud Centre, Gate A, 1st Floor.
Prince: Mohamed Bin Abdulaziz St.
Phone: 0096612 2847190 ext. 221 or 105
Mobile: 00966561968563
Email: hazem.dajani@roche.com
jeddah.drug_safety@roche.com

Hazem Dajani	Tamer Elmahallawy	Faisal Al-Samran
Local Safety Responsible	Medical Director	Regulatory Directors
H. Dajani 2/9/2015	2 2015	6/9/2015