Healthcare Provider Brochure

Actemra® (tocilizumab)

Healthcare Provider Brochure for the following indications:

- Rheumatoid Arthritis [Intravenous or subcutaneous]
- Giant Cell Arteritis [Subcutaneous]
- Polyarticular Juvenile Idiopathic Arthritis (also referred to as Juvenile Idiopathic Polyarthritis) [Intravenous or subcutaneous]
- Systemic Juvenile Idiopathic Arthritis [Intravenous or subcutaneous]

This document is approved by The Executive Directorate of Pharmacovigilance, at Saudi Food and Drug Authority [SFDA].

This Healthcare Provider Brochure contains important safety information that you need to be aware of before and during treatment with Actemra. This Healthcare Provider Brochure must be read together with the Actemra Package Leaflet and the Actemra Dosing Guide provided with this document as it contains important information about Actemra including Instructions for Use.

1. OBJECTIVE

These materials describe recommendations to minimize or prevent important risks of Actemra in patients with rheumatoid arthritis, giant cell arteritis and polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis

Consult the SPC before prescribing, preparing or administering Actemra

2. SERIOUS INFECTIONS

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including Actemra. Inform patients and parents/guardians that Actemra may lower the patient's resistance to infections. Instruct the patient and their parents/guardians to **seek immediate medical attention** if signs or symptoms suggesting infection appear in order to ensure rapid evaluation and appropriate treatment.

Actemra treatment should not be initiated in patients with active or suspected infections. Actemra may lessen signs and symptoms of acute infection, delaying the diagnosis. Timely and appropriate measures should be implemented to address serious infections. Please refer to the Special Warnings and Precautions for use (SPC section 4.4) for additional details.

3. HYPERSENSITIVITY REACTIONS

Inform the patient and parents/guardians of the patient that serious allergic reactions including anaphylaxis have been reported in association with Actemra IV and SC. Such reactions may be more severe, and potentially fatal, in patients who have experienced allergic reactions during previous treatment with Actemra even if they have received premedication with steroids and antihistamines. Most allergic reactions occur during infusion/injection or within 24 hours of Actemra administration, although allergic reactions can occur at any time.

Fatal anaphylaxis has been reported after marketing authorization during treatment with intravenous Actemra.

Instruct the patient and their parents/guardians to **seek immediate medical attention** if signs or symptoms suggesting a systemic allergic reaction appear in order to ensure rapid evaluation and appropriate treatment.

During the Actemra IV infusion, watch the patient closely for any signs and symptoms of hypersensitivity, including anaphylaxis.

If an anaphylactic reaction or other serious hypersensitivity reaction occurs, Actemra IV or SC administration should be stopped immediately, appropriate therapy initiated and Actemra should be permanently discontinued.

Patients and/or the parents/guardians of RA, pJIA, GCA and sJIA patients should be assessed for their suitability to use Actemra SC at home.

Instruct the patients or the parents/guardians of RA, pJIA, GCA and sJIA patients who are administering Actemra **to seek immediate medical attention** if they or their child experience any symptoms suggestive of an allergic reaction after receiving Actemra, and **not to** give the next dose until they have informed their doctor **AND** their doctor has told them to give the next dose.

4. COMPLICATION OF DIVERTICULITIS (INCLUDING GASTROINTESTINAL PERFORATION)

Inform patients and parents/guardians of patients that some patients who have been treated with Actemra have had serious side effects in the stomach and intestines. **Instruct the** patients and parents/guardians of patients **to seek immediate medical attention** if signs or symptoms of severe, persistent abdominal pain, hemorrhage and/or unexplained change in bowel habits with fever appear, to ensure rapid evaluation and appropriate treatment.

Actemra should be used with caution in patients with previous history of intestinal ulceration or diverticulitis, which can be associated with gastrointestinal perforation. Please refer to the Special Warnings and Precautions for use (SPC section 4.4) for additional details.

5. DIAGNOSIS OF MAS IN SJIA

Macrophage activation syndrome (MAS) is a serious life-threatening disorder that may develop in sJIA patients.

There are currently no universally accepted definitive diagnostic criteria, although preliminary criteria have been published.[1]

The differential diagnosis of MAS is broad because of the variable and multi-system abnormalities of the disorder and the non-specific nature of the most prominent clinical features, which include fever, hepatosplenomegaly and cytopenia. As a result, achieving a rapid clinical diagnosis is often difficult. Other features of MAS include neurologic abnormalities, and laboratory abnormalities such as hypofibrinogenaemia. Successful treatment of MAS has been reported with cyclosporine and glucocorticoids.

The severity and life-threatening nature of this complication, coupled with the frequent difficulties in achieving a rapid diagnosis, necessitate appropriate vigilance and careful management of patients with active sJIA.

5.1 IL-6 INHIBITION AND MAS

Some of the laboratory features associated with Actemra administration related to IL-6 inhibition are similar to some of the laboratory features associated with the diagnosis of MAS (such as a decline in leukocyte count, neutrophil count, platelet count, serum fibrinogen and erythrocyte sedimentation rate, all of which occur most notably within the week following Actemra administration). Ferritin levels

[1] Ravelli A, et al. Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. J Pediatr 2005; **146**: 598–604.

frequently decrease with Actemra administration, but often increase with MAS and, therefore, may be a useful differential laboratory parameter.

Characteristic clinical findings of MAS (central nervous system dysfunction, haemorrhage and hepatosplenomegaly), if present, are useful in establishing the diagnosis of MAS in the context of IL-6 inhibition. Clinical experience and the clinical status of the patient, coupled with the timing of the laboratory specimens in relation to Actemra administration, must guide interpretation of these laboratory data and their potential significance in making a diagnosis of MAS.

In clinical trials, Actemra has not been studied in patients during an episode of active MAS.

6. HAEMATOLOGICAL ABNORMALITIES: THROMBOCYTOSRCIA AND THE POTENTIAL RISK OF BLEEDING AND/OR NEUTROPENIA

Decreases in neutrophil and platelet counts have occurred following treatment with Actemra 8 mg/kg in combination with MTX. There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist. Severe neutropenia may be associated with an increased risk of serious infections, although there has been no clear association between decreases in neutrophils and the occurrence of serious infections in clinical trials with Actemra to date.

In patients not previously treated with Actemra, initiation is not recommended in patients with an ANC below 2 x 10^9/L. Caution should be exercised when considering initiation of Actemra treatment in patients with a low platelet count (i.e. platelet count below 100 x 10^3/ µL). In patients who develop an ANC < 0.5 x 10^9/L or a platelet count < 50 x 10^3/µL, continued treatment is not recommended.

Monitoring:

- In RA and GCA patients, neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice.
- In sJIA and pJIA patients, neutrophils and platelets should be monitored at the time of second infusion and thereafter according to good clinical practice.

Additional recommendation for neutropenia and thrombocytopenia can be found in Special warnings and precautions for use section 4.4 of the SPC.

Details on dose modification and additional monitoring can be found in the Posology and Method of administration section 4.2 of the SPC.

7. HEPATOTOXICITY

Transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with Actemra treatment (see section 4.8 of the SPC). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with Actemra. When clinically indicated, other liver function tests including bilirubin should be considered.

Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, have been observed with Actemra (see section 4.8 of the SPC). Serious hepatic injury occurred between 2 weeks

to more than 5 years after initiation of Actemra. Cases of liver failure resulting in liver transplantation have been reported.

Caution should be exercised when considering initiation of Actemra treatment in patients with elevated ALT or AST > 1.5 x ULN. In patients with baseline ALT or AST > 5 x ULN, treatment is not recommended.

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Monitoring:

- In RA, GCA, pJIA and sJIA patients, ALT/AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter.
- For recommended modifications, including Actemra discontinuation, based on transaminases levels see section 4.2 of the SPC.
- For ALT or AST elevations > 3–5 x ULN, confirmed by repeat testing, Actemra treatment should be interrupted.

Please see sections 4.2 Posology and Method of Administration, 4.4 Special warnings and precautions for use, and 4.8 Undesirable Effects of the SPC for further information.

8. ELEVATED LIPID LEVELS AND POTENTIAL RISK OF CARDIOVASCULAR/CEREBROVASCULAR EVENTS

Elevations in lipid parameters including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were observed in patients treated with Actemra.

Monitoring:

- Assessment of lipid parameters should be performed 4 to 8 weeks following initiation of Actemra therapy.

Patients should be managed according to local clinical guidelines for management of hyperlipidaemia. Please see sections 4.4 Special warnings and precautions for use and 4.8 Undesirable Effects of the SPC for further information.

9. MALIGNANCIES

Immunomodulatory medicinal products may increase the risk of malignancy. Healthcare professionals should be aware of the need for timely and appropriate measures to diagnose and treat malignancies.

Please see sections 4.4 Special warnings and precautions for use and 4.8 Undesirable Effects of the SPC for further information.

10. DEMYELINATING DISORDERS

Physicians should be vigilant for symptoms potentially indicative of new onset central demyelinating disorders. Health care providers should be aware of the need for timely and appropriate measures to diagnose and treat demyelinating disorders. Please see sections 4.4 Special warnings and precautions for use of the SPC for further information.

11. INFUSION/INJECTION REACTIONS

Serious injection/infusion site reactions may occur when administering Actemra. Recommendations for management of infusion/injection reactions can be found in Special Warnings and Precautions for Use, section 4.4 of the Actemra SPC, as well as the Actemra Dosing Guide.

12. DOSE INTERRUPTION IN SJIA AND PJIA

Recommendations for dose interruptions in sJIA and pJIA patients can be found in Posology and Method of administration section 4.2 of the SPC.

13. DOSAGE AND ADMINISTRATION

Dose calculations for all indications and formulations (IV and SC) can be found in the Actemra Dosing Guide as well as the SPC.

Paediatric patients

- The safety and efficacy of Actemra subcutaneous formulation in children from birth to less than 1 year have not been established. No data are available.
- A change in dose should only be based on a consistent change in the patient's body weight over time.

sJIA Patients
Patients must have a minimum body weight of 10 kg when receiving Actemra subcutaneously.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

14. REPORTING OF SUSPECTED ADVERSE REACTIONS

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

15. GENERAL RECOMMENDATIONS

Before you administer Actemra, ask the patient or parents/guardians if the patient:

- Has an infection, is being treated for an infection or has a history of recurring infections
- Has signs of an infection, such as a fever, cough or headache, or are feeling unwell
- Has herpes zoster or any other skin infection with open sores
- Has had any allergic reactions to previous medications, including Actemra
- Has diabetes or other underlying conditions that may predispose him or her to infection
- Has tuberculosis (TB), or has been in close contact with someone who has had TB
    - As recommended for other biologic therapies in rheumatoid arthritis, patients should be screened for latent TB infection prior to starting Actemra therapy. Patients with latent TB should be treated with standard antimycobacterial therapy before initiating Actemra
- Is taking other biological drugs to treat RA, or receiving atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporine, methylprednisolone, dexamethasone, or benzodiazepines
- Has had or currently has viral hepatitis or any other hepatic disease
- Has a history of gastrointestinal ulcers or diverticulitis
- Has recently received a vaccination or is scheduled for any vaccination
- Has cancer, cardiovascular risk factors such as raised blood pressure and raised cholesterol levels or moderate-to-severe kidney function problems
- Has persistent headaches.

Pregnancy: Female patients who are of childbearing potential must use effective contraception during (and up to 3 months after) treatment. Actemra should not be used during pregnancy unless absolutely necessary.

Breast-feeding: It is unknown whether tocilizumab is excreted in human breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Actemra should be made taking into account the benefit of breast-feeding to the child and the benefit of Actemra therapy to the woman.

Patients and parents/guardians of sJIA or pJIA patients should be advised to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade (fever) suggestive of a tuberculosis infection occur during or after therapy with Actemra

Call for reporting

If the patient experiences any side effects, talk to the doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

By reporting side effects, you or the patient can help provide more information on the safety of this medicine.

Please report any suspected adverse reactions associated with the use of Actemra (Tocilizumab) in accordance with the national requirements via the national spontaneous reporting system, to:

Roche Products Saudi Arabia L.L.C.
Direct Tel. +966 12 211 4618
Mobile: +966 56 784 4692
Email: jeddah.drug_safety@roche.com
Local Safety Responsible: doha.samargandi@roche.com
www.roche.com

Or report to:

The National Pharmacovigilance and Drug Safety Centre (NPC)
Land Line: 19999.
Website: https//:ade.sfda.gov.sa
Email: npc.drug@sfda.g

For full information on all possible side effects please see the Actemra Package Leaflet.