FOR USE IN MALTA

RoActemra® (tocilizumab)

Healthcare Professional Brochure

Healthcare Provider Brochure for the following indications:

- Rheumatoid Arthritis (RA) [Intravenous or subcutaneous]
- Giant Cell Arteritis (GCA) [Subcutaneous]
- Polyarticular Juvenile Idiopathic Arthritis (pJIA) (also referred to as Juvenile Idiopathic Polyarthritis) [Intravenous or subcutaneous]
- Systemic Juvenile Idiopathic Arthritis (sJIA) [Intravenous or subcutaneous]
- Chimeric Antigen Receptor (CAR) T cell-induced severe or life-threatening Cytokine Release Syndrome (CRS) [Intravenous]

This Healthcare Professional Brochure is additional risk minimisation material and is provided by Roche Products (Ireland) Limited as a condition of the RoActemra marketing authorisation. It contains important safety information that you need to be aware of prior to prescribing RoActemra.

This Healthcare Professional Brochure must be read together with the RoActemra Summary of Product Characteristics (available on www.ema.europa.eu) and the RoActemra Dosing Guide provided with this document (and also available on www.medicines.ie) as it contains important safety information about RoActemra including Instructions for Use.

This material should be read in conjunction with the Summary of Product Characteristics (SmPC) which is available on www.ema.europa.eu and www.medicines.ie before prescribing this medicine.

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Contents

Important Risks of RoActemra

These materials describe recommendations to minimise or prevent important risks of RoActemra in patients with rheumatoid arthritis (RA), giant cell arthritis (GCA), polyarticular juvenile idiopathic arthritis (pJIA), systemic juvenile idiopathic arthritis (sJIA), and chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS).

Consult the SmPC before prescribing, preparing or administering RoActemra.

Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including RoActemra. RoActemra treatment must not be initiated in patients with active or suspected infections. Administration of RoActemra should be interrupted if the patient develops a serious infection until the infection is controlled. Healthcare professionals should exercise caution when considering the use of RoActemra in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes and interstitial lung disease) which may predispose the patient to infections.

Vigilance for the timely detection of serious infection is recommended for patients receiving RoActemra as signs and symptoms of acute inflammation may be lessened, delaying the diagnosis. The effects of tocilizumab on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Timely and appropriate measures should be implemented to address serious infections.

Inform patients and parents/guardians that RoActemra 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.

As recommended for other biologic treatments, all patients should be screened for latent tuberculosis (TB) prior to starting RoActemra therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating RoActemra. Prescribers are reminded of the risk of false negative tuberculin skin and interferon-gamma TB blood test results, especially in patients who are severely ill or immunocompromised.

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

Hypersensitivity reactions

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

Fatal anaphylaxis has been reported after marketing authorisation during treatment with RoActemra IV.

Instruct the patient and their parents/guardian 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 RoActemra IV infusion, observe the patient closely for any signs and symptoms of hypersensitivity, including anaphylaxis. Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during treatment.

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

Patients and/or their parents or guardians of RA, pJIA, GCA and sJIA patients, should be assessed for their suitability to use RoActemra SC at home. **Instruct** the patients or the parents/guardians of RA, pJIA, GCA and sJIA patients who are administering RoActemra to **seek immediate medical attention** if they or their child experience any symptoms suggestive of an allergic reaction during or after receiving RoActemra, and **not to** give the next dose until they have informed their doctor **AND** their doctor has told them to give the next dose.

Complication of diverticulitis (including gastrointestinal perforation)

Inform patients and parents/guardians of patients that complications of diverticulitis have been reported uncommonly with RoActemra. **Instruct** the patients and parents/guardians of patients to **seek immediate medical attention** if signs or symptoms of severe, persistent abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever appear, to ensure rapid evaluation and appropriate treatment.

RoActemra 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 (SmPC section 4.4) for additional details.

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.[1,2,3,4]

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.

IL-6 inhibition and MAS

Some of the laboratory features associated with RoActemra 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 RoActemra administration). Ferritin levels frequently decrease with RoActemra administration, but often increase with MAS and therefore, may be a useful differential laboratory parameter.[1,3]

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 RoActemra administration, must guide interpretation of these laboratory data and their potential significance in making a diagnosis of MAS.

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

[1] Ravelli A, et al. Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. J Pediatr 2005; 146: 598–604. [2] Sawhney S, et al. Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders. Arch Dis Child 2001; 85: 421-6. [3] Behrens EM, et al. Occult macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis. J Rheumatol 2007; 34: 1133-8. [4] Stéphan JL, et al. Reactive haemophagocytic syndrome in children with inflammatory disorders. A retrospective study of 24 patients. Rheumatology (Oxford) 2001; 40: 1285-92.

Haematological abnormalities: thrombocytopenia and the potential risk of bleeding and/or neutropenia

Decreases in neutrophil and platelet counts have occurred following treatment with RoActemra 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 RoActemra to date.

In patients not previously treated with RoActemra, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/L. Caution should be exercised when considering initiation of RoActemra 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 SmPC.

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

Hepatotoxicity

Transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with RoActemra treatment (see section 4.8 of the SmPC). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with RoActemra. 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 RoActemra (see section 4.8 of the SmPC). Serious hepatic injury occurred between 2 weeks to more than 5 years after initiation of RoActemra. Cases of liver failure resulting in liver transplantation have been reported. Patients should be advised to immediately seek medical help if they experience signs and symptoms of hepatic injury.

Caution should be exercised when considering initiation of RoActemra 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.

Monitoring:

- In RA, GCA, pJIA and sJIA patients, ALT/AST levels 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 RoActemra discontinuation, based on transaminases levels see section 4.2 of the SmPC.
- For ALT or AST elevations >3 to 5 x ULN, confirmed by repeat testing, RoActemra 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 SmPC for further information.

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 RoActemra. In the majority of patients, there was no increase in atherogenic indices, and elevations in total cholesterol responded to treatment with lipid lowering agents.

Monitoring:

- Assessment of lipid parameters should be performed 4 to 8 weeks following initiation of RoActemra 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 SmPC for further information.

Malignancies

The risk of malignancy is increased in patients with RA. 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 SmPC for further information.

Demyelinating disorders

Physicians should be vigilant for symptoms potentially indicative of new onset central demyelinating disorders. The potential for central demyelination with RoActemra is currently unknown. Please see sections 4.4 Special warnings and precautions for use of the SmPC for further information.

Infusion/injection reactions

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

Dose interruption in sJIA and pJIA (applicable to the IV formulation & subcutaneous pre-filled syringe)

Dose adjustments due to laboratory abnormalities (sJIA and pJIA)

If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many comorbid conditions that may affect laboratory values in sJIA or pJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.

- Liver enzyme abnormalities

Laboratory Value	Action
>1 to 3 x ULN	Modify the dose of the concomitant MTX if appropriate. For persistent increases in this range, interrupt RoActemra until ALT/AST have normalised.
>3 x ULN to 5 x ULN	Modify the dose of the concomitant MTX if appropriate. Interrupt RoActemra dosing until <3 x ULN and follow recommendations above for >1 to 3 x ULN.
>5 x ULN	Discontinue RoActemra. The decision to discontinue RoActemra in sJIA or pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low absolute neutrophil count (ANC)

Laboratory Value (cells x 10^9/L)	Action
ANC >1	Maintain dose.
ANC 0.5 to 1	Interrupt RoActemra dosing. When ANC increases to >1 x 10^9/L resume RoActemra.
ANC <0.5	Discontinue RoActemra. The decision to discontinue RoActemra in sJIA or pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low platelet count

Laboratory Value (cells x 10^3/µL)	Action
50 to 100	Modify the dose of the concomitant MTX if appropriate. Interrupt RoActemra dosing. When platelet count is >100 x 10^3/µL resume RoActemra.
<50	Discontinue RoActemra. The decision to discontinue RoActemra in sJIA or pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

Reduction of tocilizumab dosing frequency due to laboratory abnormalities has not been studied in pJIA patients.

There are insufficient clinical data to assess the impact of a tocilizumab dose reduction in sJIA patients who have experienced laboratory abnormalities. Available data suggest that clinical improvement is observed within 6 weeks of initiation of treatment with RoActemra. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe.

The safety and efficacy of RoActemra subcutaneous formulation in children with conditions other than sJIA or pJIA have not been established.

Available data with the IV formulation suggest that clinical improvement is observed within 12 weeks of initiation of treatment with RoActemra. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe.

Dosage and administration

Dose calculations for all indications and formulations (IV and SC) can be found in the RoActemra Dosing Guide as well as section 4.2 of the SmPC.

Paediatric patients

- The safety and efficacy of RoActemra 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.
- The pre-filled pen (ACTPen) should not be used to treat paediatric patients < 12 years of age since there is a potential risk of intramuscular injection due to thinner subcutaneous tissue layer.

sJIA Patients

Patients must have a minimum body weight of 10 kg when receiving RoActemra 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.

General Recommendations

Before you administer RoActemra, 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 is feeling unwell
- Has herpes zoster or any other skin infection with open sores
- Has had any allergic reactions to previous medications, including RoActemra
- Has diabetes or other underlying conditions that may predispose him or her to infection
- Has or has had tuberculosis (TB), or has been in close contact with someone who has had TB
  - RA, GCA, sJIA and pJIA patients should be screened for latent TB infection prior to starting RoActemra therapy. Patients with latent TB should be treated with standard anti mycobacterial therapy before initiating RoActemra
- Is taking other biological drugs to treat RA, sJIA, pJIA or GCA 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. RoActemra 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 RoActemra should be made taking into account the benefit of breast-feeding to the child and the benefit of RoActemra 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 RoActemra.

Call for Reporting

Reporting of suspected adverse events or reactions

Reporting suspected adverse events or reactions after authorisation 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 events or reactions (see details below).

Where possible, healthcare professionals should report adverse events or reactions by brand name and batch number.

In the event of a suspected adverse event, please report it to:
Post: The Drug Surveillance Centre, Roche Products (Ireland) Limited,
3004 Lake Drive, Citywest, Naas Road, Dublin 24, Ireland.
Telephone: 00 353 (0)1 4690700
Email: ireland.drug_surveillance_centre@roche.com

Alternatively, suspected adverse reactions or medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at:
http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to:
Post: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority,
Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta.
Email: postlicensing.medicinesauthority@gov.mt

Further Information

For electronic copies of this risk minimisation material, refer to the Malta Medicines Authority website [http://www.medicinesauthority.gov.mt/rmm] and download the required material.
Alternatively if you would like hard copies, please contact Roche Products (Ireland) Limited, 3004 Lake Drive, Citywest, Naas Road, Dublin 24 by mail, telephone [00 353 (0)1 4690700] or email [ireland.drug_surveillance_centre@roche.com].

For further information about this medicine, please contact Medical Information at Roche Products (Ireland) Limited by telephone [00 353 (0)1 4690700] or email [Ireland.druginfo@roche.com].

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