RoActemra® (tocilizumab)

Healthcare Professional Brochure

RoActemra® (tocilizumab) for the following indications:

- Rheumatoid Arthritis (RA)
- Giant Cell Arteritis (GCA)
- Polyarticular Juvenile Idiopathic Arthritis (pJIA)
- Systemic Juvenile Idiopathic Arthritis (sJIA)
- Chimeric Antigen Receptor (CAR) T cell-induced severe or life-threatening Cytokine Release Syndrome (CRS)

This educational material is provided by Roche Products (Ireland) Limited and is mandatory as a condition of the Marketing Authorisation in order to further minimise important selected risks.

Detailed information on this medicine is available on the European Medicines Agency website (www.ema.europa.eu) and www.medicines.ie

MT v24.1.0
Date of Malta Medicines Authority Approval: August 2019

Indications and usage

RoActemra Intravenous (IV)

- RoActemra IV, in combination with methotrexate (MTX), is indicated for:
  - the treatment of severe, active and progressive RA in adults not previously treated with MTX.
  - the treatment of moderate-to-severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.
- In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.
- RoActemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with MTX.
- RoActemra is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.
- RoActemra in combination with MTX is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.
- RoActemra is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older.

RoActemra Subcutaneous (SC) – Pre-Filled Syringe (PFS)

- RoActemra SC, in combination with methotrexate (MTX), is indicated for:
  - the treatment of severe, active and progressive RA in adults not previously treated with MTX.
  - the treatment of moderate-to-severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.
- In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.
- RoActemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with MTX.
- RoActemra is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.
- RoActemra in combination with MTX is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.
- RoActemra is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients.

RoActemra SC – Autoinjector (ACTPen)

- RoActemra, in combination with methotrexate (MTX), is indicated for:
  - the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
  - the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.
- In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.
- RoActemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with MTX.
- RoActemra is indicated for the treatment of GCA in adult patients.

Important Risks of RoActemra

This section describes recommendations to minimise or prevent important risks of RoActemra in patients with RA, GCA, pJIA, sJIA, and CAR T cell-induced severe or life-threatening 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. Inform patients and parents/guardians that RoActemra may lower their resistance to infections. Instruct the patient and their parents/guardian to **seek immediate medical attention** if signs or symptoms suggesting infection appear in order to ensure rapid evaluation and appropriate treatment.

RoActemra treatment must not be initiated in patients with active or suspected infections. RoActemra 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 (SmPC section 4.4) for additional details.

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 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 infusion, watch the patient closely for any signs and symptoms of hypersensitivity, including anaphylaxis. 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, should be assessed for their suitability to use RoActemra SC at home. Patients who are self-administering RoActemra should be advised to **seek immediate medical attention** if they experience any symptoms suggestive of an allergic reaction. They should not take the next dose until they have informed you (their doctor/HCP) and you have told them to take the next dose.

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

Complication of diverticulitis (including gastrointestinal perforation)

Inform patients and parents/guardians of patients that some patients who have been treated with RoActemra have had serious side effects in the stomach and intestines. Instruct the patient 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.

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.

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.

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.

Liver enzyme and bilirubin elevations and potential risk of hepatotoxicity

Transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with RoActemra treatment, without progression to hepatic injury. An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with RoActemra.

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 and GCA patients**, ALT and AST levels should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For ALT or AST elevations > 3 to 5 x ULN, RoActemra treatment should be interrupted.
- **In pJIA and sJIA patients**, ALT and AST should be monitored at the time of the second administration and thereafter according to good clinical practice.
- When clinically indicated, other liver function tests, including bilirubin should be considered.

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.

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

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. Healthcare 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 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

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

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.

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 tuberculosis (TB), or has been in close contact with someone who has had TB
  - As recommended for other biologic therapies in RA, patients should be screened for latent TB infection prior to starting RoActemra therapy. Patients with latent TB should be treated with standard antimycobacterial therapy before initiating RoActemra
- 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. 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.

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:
The Drug Surveillance Centre, Roche Products (Ireland) Limited,
3004 Lake Drive, Citywest, Naas Road, Dublin 24.
Telephone: 00 353 (0)1 4690700
Fax: 00 353 (0)1 4690793
Email: ireland.drug_surveillance_centre@roche.com

Alternatively, suspected adverse reactions should be reported to:
Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority,
Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta.
Reporting forms and information can be found at www.medicinesauthority.gov.mt/adrportal

Further Information

For additional copies of this risk minimisation material, refer to the Malta Medicines Authority website [http://www.medicinesauthority.gov.mt/rmm] and download the required material or 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], fax [00 353 (0)1 4690793] 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], fax [00 353 (0)1 4690793] or email [Ireland.druginfo@roche.com].

MT v24.1.0
Date of Malta Medicines Authority Approval: August 2019