

# Important Efficacy and Safety Information for Healthcare Professionals

RoActemra<sup>®</sup> (tocilizumab) for Systemic Juvenile  
Idiopathic Arthritis (sJIA) and Polyarticular Juvenile  
Idiopathic Arthritis (pJIA)

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Full prescribing information can be found in the RoActemra Summary of Product Characteristics (SmPC) [www.medicines.org.uk](http://www.medicines.org.uk)

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## Indication and usage for patients with sJIA and pJIA

### sJIA (RoActemra IV)

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 non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to methotrexate [MTX] or where treatment with MTX is inappropriate) or in combination with MTX.

The efficacy of IV RoActemra for the treatment of active sJIA was assessed in a 12 week Phase III, randomised, double-blind, placebo-controlled, parallel-group, two-arm study (TENDER study).

### pJIA (RoActemra IV or SC)

RoActemra in combination with methotrexate (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.

The efficacy of IV RoActemra for the treatment of active pJIA was assessed in a three-part study (CHERISH study). Part I consisted of a 16-week active RoActemra treatment lead-in period, followed by Part II, a 24-week randomised double-blind placebo-controlled withdrawal period, followed by Part III, a 64-week open-label period.

A 52-week, open-label, multicentre study (Study WA28117) assessed the appropriate SC dose of RoActemra that achieved comparable PK/PD and safety profiles to the IV regimen, in patients with active pJIA.

## Patient counselling information and laboratory monitoring

### Patient counselling information

Before initiating therapy, patients and parents/guardians of sJIA and pJIA patients should be advised of the potential risks and benefits of RoActemra.

The potential risks associated with RoActemra treatment

#### • Infections:

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including RoActemra. Inform patients and parents/guardians of sJIA and pJIA patients 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. Signs or symptoms of infection may include:

- Fever
- Persistent cough
- Weight loss
- Throat pain or soreness
- Wheezing
- Red or swollen skin blisters, skin tears or wounds
- Severe weakness or tiredness

#### • Hypersensitivity reactions:

Inform the patient and parents/guardians of sJIA and pJIA patients that serious allergic reactions including anaphylaxis have been reported in association with RoActemra. 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 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.

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. Possible signs or symptoms of a systemic allergic reaction include:

- Rash, itching or hives
- Chest pain
- Feeling dizzy or faint
- Hypotension
- Shortness of breath or trouble breathing
- Swelling of the lips, tongue or face
- Severe stomach pain or vomiting

### RoActemra IV



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 should be stopped immediately, appropriate therapy initiated and RoActemra permanently discontinued.

### RoActemra SC



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

Patients, parents/guardians, who are administering RoActemra SC at home, should be advised to **seek urgent medical attention** if the patient experiences any symptom suggestive of an allergic reaction. The patient should not take the next dose until you (their doctor/HCP) have been informed and you have told them to take the next dose.

Self-administration is not recommended in children with pJIA. Administration should be done by a healthcare professional or parent /guardian/caregiver.

#### • Vaccinations:

Inform patients and parents/guardians of sJIA and pJIA patients that any live or live-attenuated vaccines should not be received during RoActemra therapy. Patients should be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating RoActemra therapy. The interval between live vaccinations and initiation of RoActemra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

#### • Gastrointestinal side effects:

Inform patients and parents/guardians of sJIA and pJIA patients that some patients who have been treated with RoActemra have had serious side effects on the stomach and intestines including diverticulitis. Instruct patients and parents/guardians of sJIA and pJIA patients, that patients should **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.

Before you administer RoActemra, ask the patient or parents/guardians of sJIA and pJIA patients 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
- Is a young woman of childbearing age and may be pregnant or sexually active. Female patients of childbearing potential must use effective contraception during (and up to 3 months after) treatment. RoActemra should not be used during pregnancy unless clearly necessary
- 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 biological treatments, sJIA/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 sJIA/pJIA, or receiving atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, ciclosporin or benzodiazepines
- Has had or currently has viral hepatitis or another hepatic disease
- Has a history of gastrointestinal ulcers or diverticulitis
- Has recently received a vaccination or are 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 a history of macrophage activation syndrome (MAS) (Only relevant to sJIA patients)

### Laboratory monitoring

Alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels, neutrophils and platelets should be monitored at the time of the second administration and thereafter according to good clinical practice (see section Warning and Precautions, Laboratory parameters).

## Clinical response

### The potential benefits associated with RoActemra treatment

#### RoActemra IV in pJIA



In the CHERISH study, 48.1% (39/81) of placebo-treated patients and 25.6% (21/82) of RoActemra-treated patients had a JIA ACR30 flare by Week 40 relative to Week 16 (primary endpoint). These proportions were statistically significantly different ( $p=0.0024$ ). The percentages of patients achieving JIA ACR30, 50 and 70 responses are shown below.

#### CHERISH: JIA ACR response rates at Week 40 relative to baseline (percentage of patients)

Response rate	RoActemra n=82	Placebo n=81
JIA ACR30	74.4%*	54.3%*
JIA ACR50	73.2%*	51.9%*
JIA ACR70	64.6%*	42.0%*

\* $p<0.01$ , RoActemra vs. placebo

The number of active joints was significantly reduced compared with baseline in patients receiving RoActemra compared with placebo ( $p=0.0435$ ), as was the physician's global assessment of disease activity ( $p=0.0031$ ).

The adjusted mean change in the pain visual analogue scale (VAS) after 40 weeks of RoActemra treatment was 32.4 mm on a 0–100 mm scale compared with a reduction of 22.3 mm for placebo patients. This greater reduction in pain on RoActemra in comparison with placebo was highly statistically significant ( $p=0.0076$ ).

#### RoActemra IV in sJIA



In the TENDER study, 85% (64/75) of RoActemra-treated patients and 24% (9/37) of placebo-treated patients achieved the primary endpoint of at least 30% improvement in the JIA ACR core set (JIA ACR30 response) and absence of fever (no temperature recording  $\geq 37.5^\circ\text{C}$  in the preceding 7 days) at Week 12. These proportions were highly significantly different ( $p<0.0001$ ).

The percentages of patients achieving JIA ACR30, 50, 70 and 90 responses are shown below. Responses are maintained in the ongoing open-label extension phase.

**TENDER: JIA ACR response rates at Week 12 (% patients)**

Response rate	RoActemra n=75	Placebo n=37
JIA ACR30	90.7%*	24.3%
JIA ACR50	85.3%*	10.8%
JIA ACR70	70.7%*	8.1%
JIA ACR90	37.3%*	5.4%

\*p<0.0001, RoActemra vs. placebo

**Systemic effects**

In the RoActemra-treated patients, 85% who had fever due to sJIA at baseline were free of fever (no temperature recording  $\geq 37.5^{\circ}\text{C}$  in the preceding 14 days) at Week 12 versus only 21% of placebo-treated patients (p<0.0001).

The adjusted mean change in the pain visual analogue scale (VAS) after 12 weeks of RoActemra treatment was a reduction of 41 points on a scale of 0–100 compared to a reduction of 1 for placebo-treated patients (p<0.0001).

**Corticosteroid tapering**

Patients achieving a JIA ACR70 response were permitted corticosteroid dose reduction. Seventeen (24%) RoActemra-treated patients versus one (3%) placebo-treated patient were able to reduce their corticosteroid dose by at least 20% without experiencing a subsequent JIA ACR30 flare or occurrence of systemic symptoms to Week 12 (p=0.028). Reductions in corticosteroids continued, with 44 patients off oral corticosteroids at Week 44, while maintaining JIA ACR responses.

**Health-related and quality-of-life outcomes**

At Week 12, the proportion of RoActemra-treated patients showing a minimally clinically important improvement in the Childhood Health Assessment Questionnaire – Disability Index (defined as an individual total score decrease of  $\geq 0.13$ ) was significantly higher than in placebo-treated patients, 77% versus 19% (p<0.0001).

**Laboratory parameters**

In the RoActemra-treated patients, 67% (50/75) had a haemoglobin less than the lower limit of normal (LLN) at baseline and 80% (40/50) of these patients had an increase in their haemoglobin to within the normal range at Week 12, in comparison to only 7% (2/29) of placebo-treated patients with haemoglobin <LLN at baseline (p<0.0001).

**RoActemra SC in pJIA**



In Study WA28117, eligible patients received RoActemra dosed according to body weight (BW), with patients weighing  $\geq 30$  kg (n =25) dosed with 162 mg of RoActemra every 2 weeks (Q2W) and patients weighing below 30 kg (n =27) dosed with 162 mg of RoActemra every 3 weeks (Q3W) for 52 weeks. Of these 52 patients, 37 (71%) were naive to RoActemra and 15 (29%) had been receiving RoActemra IV and switched to RoActemra SC at baseline.

The RoActemra SC regimens of 162 mg Q3W for patients weighing below 30 kg and of 162 mg Q2W for patients weighing  $\geq 30$  kg respectively provide PK exposure and PD responses to support efficacy and safety outcomes similar to those achieved with the approved RoActemra IV regimens for pJIA.

Exploratory efficacy results showed that RoActemra SC improved median Juvenile Arthritis Disease Activity Score (JADAS)-71 for RoActemra naive patients and maintained the median JADAS-71 for patients who switched from IV to SC RoActemra treatment over the entire course of the study for patients in both body weight groups (below 30 kg and  $\geq 30$  kg).

**Warnings and precautions**

**Infections**

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including RoActemra. RoActemra treatment should not be initiated in patients with active infections. Administration of RoActemra should be interrupted if a 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 patients to infections.

Vigilance for the timely detection of serious infection is recommended for patients receiving immunosuppressive agents such as RoActemra for active sJIA and pJIA, as signs and symptoms of acute inflammation may be lessened, associated with suppression of the acute-phase reaction. The effects of RoActemra on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection.

**Patients (including younger children with sJIA and pJIA who may be less able to communicate their symptoms) and parents/guardians should be instructed to contact their healthcare professional immediately if any symptoms suggesting infection appear, in order to ensure rapid evaluation and appropriate treatment.**

## Tuberculosis

As recommended for other biological treatments, sJIA and pJIA patients should be screened for latent tuberculosis (TB) infection 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 with sJIA and pJIA should be instructed 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.**

## Viral reactivation

Viral reactivation (e.g. hepatitis B virus) has been reported with biologic therapies for rheumatoid arthritis (RA). In clinical studies with RoActemra, patients who screened positive for hepatitis were excluded.

## Complications of diverticulitis

Events of diverticular perforations as complications of diverticulitis have been reported uncommonly with RoActemra. RoActemra should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis, which can be associated with gastrointestinal perforation.

## Hypersensitivity reactions

Serious hypersensitivity reactions have been reported in association with RoActemra. Such reactions may be more severe, and potentially fatal, in patients who have experienced hypersensitivity reactions during previous treatment with RoActemra even if they have received premedication with steroids and antihistamines. Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during treatment with RoActemra. If an anaphylactic reaction or other serious hypersensitivity/serious infusion-related reaction occurs, administration of RoActemra should be stopped immediately and RoActemra should be permanently discontinued. Fatal anaphylaxis has been reported after marketing authorisation during treatment with RoActemra.

## Active hepatic disease and hepatic impairment

Treatment with RoActemra, particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases; therefore, caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment.

## Laboratory parameters

### Neutrophils

Decreases in neutrophil counts have occurred following treatment with RoActemra. There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist.

In patients not previously treated with RoActemra, initiation is not recommended in patients with an absolute neutrophil count (ANC) below  $2 \times 10^9/l$ . In patients who develop an ANC  $<0.5 \times 10^9/l$ , continued treatment is not recommended.

Severe neutropenia may be associated with an increased risk of serious infections. Infections have been reported in neutropenic patients. Neutrophils should be monitored at the time of second administration and thereafter according to good clinical practice.

Low absolute neutrophil count (ANC)		
Laboratory value (cells $\times 10^9/L$ )	Action	
ANC $> 1$	Maintain RoActemra dose	
ANC 0.5 to 1	RoActemra IV	RoActemra SC
	Interrupt RoActemra dosing When ANC increases to $>1 \times 10^9/l$ resume RoActemra	Interrupt RoActemra dosing When ANC increases to $> 1 \times 10^9/L$ resume RoActemra
ANC $< 0.5$	Discontinue RoActemra The decision to discontinue RoActemra for a laboratory abnormality should be based on the medical assessment of the individual patient	Discontinue RoActemra The decision to discontinue RoActemra in pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient

### Platelets

Decreases in platelet counts have occurred following treatment with RoActemra.

Caution should be exercised when considering initiation of RoActemra treatment in patients with a low platelet count (i.e. platelet count below  $100 \times 10^3/\mu l$ ). In patients who develop a platelet count  $<50 \times 10^3/\mu l$ , continued treatment is not recommended.

Platelets should be monitored at the time of second administration and thereafter according to good clinical practice.



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

#### Hepatic transaminases

In clinical trials, 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. When clinically indicated, other liver function tests including bilirubin should be considered.

Caution should be exercised when considering initiation of RoActemra treatment in patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5 x upper limit of normal (ULN). In patients with baseline ALT or AST >5 x ULN, treatment is not recommended. ALT and AST levels should be monitored at the time of the second administration and thereafter according to good clinical practice.

Liver enzyme abnormalities		
Laboratory value	Action	
	RoActemra IV	RoActemra SC
>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	Modify the dose of the concomitant MTX if appropriate For persistent increases in this range, interrupt RoActemra until ALT/AST have normalised
>3 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	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 pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient	Discontinue RoActemra The decision to discontinue RoActemra in pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient

#### Lipids

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

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.

#### Neurological 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.

#### Malignancy

Immunomodulatory medicinal products may increase the risk of malignancy.

#### Vaccinations

Live and live-attenuated vaccines should not be given concurrently with RoActemra as clinical safety has not been established. It is recommended that sJIA and pJIA patients be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating RoActemra therapy. The interval between live vaccinations and initiation of RoActemra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

#### Cardiovascular risk in sJIA/pJIA patients

Patients with sJIA/pJIA should have risk factors (e.g. hypertension, hyperlipidaemia) managed as part of usual standard of care.

#### Combination with TNF antagonists

There is no experience of the use of RoActemra with TNF antagonists or other biological treatments for sJIA/pJIA patients. RoActemra is not recommended for use with other biological agents.

#### Macrophage activation syndrome (MAS)

MAS is a serious life-threatening disorder that may develop in sJIA patients. In clinical trials, RoActemra has not been studied in patients during an episode of active MAS.

#### Product 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.

## Undesirable effects

In general, the adverse drug reactions (ADRs) in sJIA /pJIA patients were similar in type to those seen in RA patients.

Summary of the ADRs occurring in patients with pJIA and sJIA receiving IV RoActemra as monotherapy or in combination with MTX

System organ class	Preferred Term	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Infections and infestations	Upper respiratory tract infections	pJIA, sJIA		
	Nasopharyngitis	pJIA, sJIA		
Gastrointestinal disorders	Nausea		pJIA	
	Diarrhoea		pJIA, sJIA	
General disorders and administration site conditions	Infusion related reactions		pJIA <sup>1</sup> , sJIA <sup>2</sup>	
Nervous system disorders	Headache	pJIA	sJIA	
Investigations	Hepatic transaminases increased		pJIA	
	Decrease in neutrophil count	sJIA	pJIA	
	Platelet count decreased		sJIA	pJIA
	Cholesterol increased		sJIA	pJIA

1. Infusion related reaction events in pJIA patients included but were not limited to headache, nausea and hypotension

2. Infusion related reaction events in sJIA patients included but were not limited to rash, urticaria, diarrhoea, epigastric discomfort, arthralgia and headache.

### RoActemra IV in sJIA



#### Infections

In the 12-week controlled clinical study, the rate of all infections in the RoActemra group was 344.7 per 100 patient-years compared with 287.0 per 100 patient-years in the placebo group.

In the open-label extension study, the overall rate of infections remained similar at 306.6 per 100 patient-years.

In the 12-week controlled clinical study, the rate of serious infections in the RoActemra group was 11.5 per 100 patient-years. In the open-label extension study, the overall rate of serious infections remained stable at 11.3 per 100 patient-years. Reported serious infections were similar to those seen in RA patients with the addition of varicella and otitis media.

#### Infusion reactions

Infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion. In the 12-week controlled clinical study, 4% of patients from the RoActemra group

experienced events occurring during infusion. One event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment.

In the RoActemra group, 16% of patients experienced an event within 24 hours of infusion compared to 5.4% of patients in the placebo group during the 12-week clinical study. In the RoActemra group, the events included, but were not limited to, rash, urticaria, diarrhoea, epigastric discomfort, arthralgia and headache. One of these events, urticaria, was considered serious.

Clinically significant hypersensitivity reactions associated with RoActemra and requiring treatment discontinuation were reported in <1% (1 out of 112) patients treated with RoActemra during the controlled and open-label clinical study.

#### Immunogenicity

All 112 patients were tested for anti-RoActemra antibodies at baseline. Two patients developed positive anti-RoActemra antibodies, with one of these patients having a hypersensitivity reaction leading to withdrawal. The incidence of anti-RoActemra antibody formation might be underestimated because of interference of RoActemra with the assay and higher drug concentration observed in children compared to adults.

#### Neutrophils

During routine laboratory monitoring in the 12-week clinical study, a decrease in neutrophil counts below  $1 \times 10^9/l$  occurred in 7% of patients in the RoActemra group, and no decreases in the placebo group. In the open-label clinical study, decreases in neutrophil counts below  $1 \times 10^9/l$  occurred in 15% of the RoActemra group.

#### Platelets

During routine laboratory monitoring in the 12-week clinical study, 3% of patients in the placebo group and 1% in the RoActemra group had a decrease in platelet count to  $\leq 100 \times 10^3/\mu l$ .

In the open-label clinical study, decreases in platelet counts below  $100 \times 10^3/\mu l$  occurred in 3% of patients in the RoActemra group, without associated bleeding events.

#### Hepatic transaminase elevations

During routine laboratory monitoring in the 12-week clinical study, elevation in ALT or AST  $\geq 3 \times$  ULN occurred in 5% and 3% of patients, respectively, in the RoActemra group, and none in the placebo group. In the open-label clinical study, elevation in ALT or AST  $\geq 3 \times$  ULN occurred in 12% and 4% of patients, respectively, in the RoActemra group.

#### Immunoglobulin G

IgG levels decrease during therapy. A decrease to the LLN occurred in 15 patients at some point in the study.

#### Lipid parameters

During routine laboratory monitoring in the 12-week clinical study, 13.4% and 33.3% of patients experienced a post-baseline elevation of their LDL-cholesterol value to  $\geq 130$  mg/dL and total cholesterol value to  $\geq 200$  mg/dL, respectively.



## Undesirable effects

### RoActemra IV in pJIA



#### Infections

Following 184.4 patient-years of exposure with RoActemra IV in pJIA patients, the rate of infection was 163.7 per 100 patient-years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was numerically higher in patients weighing <30 kg treated with 10 mg/kg RoActemra (12.2 per 100 patient years) compared to patients weighing  $\geq$ 30 kg, treated with 8 mg/kg RoActemra (4.0 per 100 patient years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing <30 kg treated with 10 mg/kg RoActemra (21.4%) compared to patients weighing  $\geq$ 30 kg, treated with 8 mg/kg RoActemra (7.6%).

#### Infusion reactions

Infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion. Following 184.4 patient-years of exposure with RoActemra in pJIA patients, 11 patients (5.9%) experienced infusion reactions during the infusion and 38 patients (20.2%) experienced an event within 24 hours of an infusion. The most common events occurring during infusion were headache, nausea and hypotension and those within 24 hours of infusion were dizziness and hypotension. In general, the adverse drug reactions observed during or within 24 hours of an infusion were similar in nature to those seen in RA and sJIA patients. No clinically significant hypersensitivity reactions requiring treatment discontinuation were reported.

#### Immunogenicity

One patient in the 10 mg/kg <30 kg group developed positive anti-RoActemra antibodies without developing a hypersensitivity reaction, and subsequently withdrew from the study.

#### Neutrophils

During routine laboratory monitoring following 184.4 patient-years of exposure with RoActemra IV in pJIA patients, a decrease in neutrophil count below  $1 \times 10^9/l$  occurred in 3.7% of patients.

#### Platelets

During routine laboratory monitoring following 184.4 patient-years of exposure with RoActemra in pJIA patients, 1% of patients had a decrease in platelet count to  $\leq 50 \times 10^3/\mu l$  without associated bleeding events.

#### Hepatic transaminase elevations

During routine laboratory monitoring following 184.4 patient-years of exposure with RoActemra in pJIA patients, elevation in ALT or AST  $\geq 3 \times$  ULN occurred in 3.7% and <1% of patients, respectively.

#### Lipid parameters

During routine laboratory monitoring following 184.4 patient-years of exposure with RoActemra in pJIA patients, elevation in total cholesterol  $>1.5-2 \times$  ULN occurred in one patient (0.5%) and elevation in LDL  $>1.5-2 \times$  ULN in one patient (0.5%).

### RoActemra SC in pJIA



The safety profile of subcutaneous RoActemra was also evaluated in 52 patients with pJIA with a total patient exposure to RoActemra SC of 50.4 patient-years. In general, the safety profile observed in patients with pJIA was consistent with the known safety profile of RoActemra with the exception of injection site reactions (ISRs). A higher frequency of pJIA patients experienced ISRs following SC RoActemra injections compared to either adult RA.

#### Infections

In the SC RoActemra study, the rates of infections in pJIA patients treated with SC RoActemra was comparable with pJIA patient treated with IV RoActemra.

#### Injection site reactions

A total of 28.8% (15/52) pJIA patients experienced ISRs to RoActemra SC. These ISRs occurred in a 44% of patients  $\geq 30$  kg compared to 14.8% of patients below 30 kg. The most common ISRs were injection site erythema, swelling, hematoma, pain and pruritis. All ISRs reported were non-serious Grade 1 events, and none of the ISRs required patient withdrawal from treatment or dose interruption.

#### Immunogenicity

In the SC Study 5.8% (3/52) developed positive neutralizing anti-RoActemra antibodies without developing a serious or clinically significant hypersensitivity reaction. Of these 3 patients, 1 subsequently withdrew from the study. No correlation between antibody development and clinical response or adverse events was observed.

### RoActemra SC in pJIA continued...



#### Neutrophils

During routine laboratory monitoring following 50.4 patient-years of exposure with RoActemra SC, a decrease in neutrophil count below  $1 \times 10^9/L$  occurred in 15.4% of patients treated.

#### Hepatic transaminase elevations

An elevation in ALT or AST  $\geq 3 \times$  ULN occurred in 9.6% and 3.8% patients treated with RoActemra SC, respectively. No patients experienced a decrease in platelet count to  $\leq 50 \times 10^3 / \mu L$ .

#### Lipid parameters

In the SC Study, 14.3% and 12.8% of patients experienced a post-baseline elevation of their LDL-cholesterol value to  $\geq 130$  mg/dL and total cholesterol value to  $\geq 200$  mg/dL at any time during study treatment, respectively.

## Drug interactions

Interaction studies have only been performed in adults.

Concomitant administration of a single dose of 10 mg/kg RoActemra with 10 to 25 mg MTX once weekly had no clinically significant effect on MTX exposure.

There is no experience of the use of RoActemra with TNF antagonists or other biological treatments for sJIA or pJIA patients. RoActemra is not recommended for use with other biological agents.

### Interactions with CYP450 substrates

The expression of hepatic CYP450 enzymes is suppressed by cytokines, such as IL-6, that stimulate chronic inflammation. Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as RoActemra, is introduced.

*In vitro* studies with cultured human hepatocytes demonstrated that IL-6 caused a reduction in CYP1A2, CYP2C9, CYP2C19 and CYP3A4 enzyme expression. RoActemra normalises expression of these enzymes.

When starting or stopping therapy with RoActemra, patients taking medicinal products which are individually adjusted and are metabolised via CYP450, CYP3A4, CYP1A2 or CYP2C9 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, ciclosporin or benzodiazepines) should be monitored as doses may need to be modified to maintain therapeutic effect. Given its long elimination half-life ( $t_{1/2}$ ), the effect of RoActemra on CYP450 enzyme activity may persist for several weeks after stopping therapy.

## Use in specific populations

### Paediatric patients

The safety and efficacy of RoActemra in children below 2 years of age has not been established and therefore RoActemra is not recommended for use in these patients.

### Renal impairment

No dose adjustment is required in patients with mild renal impairment. Renal function should be closely monitored in all patients with severe renal impairment and in paediatric patients with moderate-to-severe renal impairment; RoActemra has not been studied in these patients.

### Hepatic impairment

RoActemra has not been studied in patients with hepatic impairment. Therefore, no dose recommendations can be made.

### Pregnancy

There are no adequate data from the use of RoActemra in pregnant women. A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose. The potential risk for humans is unknown. Female patients of childbearing potential must use effective contraception during and up to 3 months after treatment.

RoActemra should not be used during pregnancy unless clearly necessary.

### Breastfeeding

It is unknown whether RoActemra is excreted in human breast milk. The excretion of RoActemra in milk has not been studied in animals. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with RoActemra should be made taking into account the benefit of breastfeeding to the child and the benefit of RoActemra therapy to the patient.

### Fertility

Available non-clinical RoActemra data do not suggest an effect on fertility.

## Dosage and administration

### RoActemra IV in sJIA



The recommended dose of RoActemra in sJIA patients is 8 mg/kg once every 2 weeks in patients weighing  $\geq 30$  kg, or 12 mg/kg once every 2 weeks in patients weighing  $< 30$  kg. The dose should be calculated based on the patient's body weight at each administration. Please refer to the Step by Step Dosing and Administration Guide for the correct dose. A change in dose should only be based on a consistent change in the patient's body weight over time.

- RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX
- There is no experience of the use of RoActemra with TNF antagonists or other biological treatments for sJIA patients. RoActemra is not recommended for use with other biological agents

#### General dose advice

- Dose interruptions of RoActemra for laboratory abnormalities are recommended
- Reduction of RoActemra dose due to laboratory abnormalities has not been studied in sJIA
  - If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and RoActemra dosing interrupted until the clinical situation has been evaluated
- The decision to discontinue RoActemra for a laboratory abnormality should be based on the medical assessment of the individual patient

#### General considerations for administration

RoActemra concentrate for intravenous (IV) infusion should be diluted by a healthcare professional using aseptic technique.

#### For patients $< 30$ kg

- From a 50 ml infusion bag, withdraw a volume of 0.9% (9 mg/ml) sterile, non-pyrogenic sodium chloride solution for injection equal to the volume of RoActemra concentrate required for the patient's dose
- The required amount of RoActemra concentrate (0.6 ml/kg) should be withdrawn from the vial and placed in the 50 ml infusion bag. This should be a final volume of 50 ml

#### For patients $\geq 30$ kg

- From a 100 ml infusion bag, withdraw a volume of 0.9% (9 mg/ml) sterile, non-pyrogenic sodium chloride solution for injection equal to the volume of RoActemra concentrate required for the patient's dose
- The required amount of RoActemra concentrate (0.4 ml/kg) should be withdrawn from the vial and placed in the 100 ml infusion bag. This should be a final volume of 100 ml

- Slowly add RoActemra concentrate for IV infusion from each vial into the infusion bag. To mix the solution, gently invert the bag to avoid foaming
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted
- After dilution, the prepared solution for infusion is physically and chemically stable in sodium chloride 9 mg/ml (0.9%) at 30°C for 24 hours. From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in use storage times and conditions are the responsibility of the user and would normally be no longer than 24 hours at 2°C–8°C, unless dilution has taken place in controlled and validated aseptic conditions. RoActemra solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used
- Allow the fully diluted RoActemra solution to reach room temperature prior to infusion
- The infusion should be administered over 60 minutes and must be administered with an infusion set. Do not administer as an IV push or bolus
- RoActemra should not be infused concomitantly in the same IV line with other drugs. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of RoActemra with other medications

### RoActemra IV in pJIA



The recommended dose of RoActemra in pJIA patients is 8 mg/kg once every 4 weeks in patients weighing  $\geq 30$  kg, or 10 mg/kg once every 4 weeks in patients weighing  $< 30$  kg. The dose should be calculated based on the patient's body weight at each administration. Please refer to the Step by Step Dosing and Administration Guide for the correct dose. A change in dose should only be based on a consistent change in the patient's body weight over time

- RoActemra can be given as monotherapy (in case of intolerance to MTX or where continued treatment with MTX is inappropriate) or in combination with MTX
- There is no experience of the use of RoActemra with TNF antagonists or other biological treatments for pJIA patients. RoActemra is not recommended for use with other biological agents.

#### General dose advice

- Dose interruptions of RoActemra for laboratory abnormalities are recommended
- Reduction of RoActemra dose due to laboratory abnormalities has not been studied in pJIA
  - If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and RoActemra dosing interrupted until the clinical situation has been evaluated
- As there are many co-morbid conditions that may affect laboratory values in pJIA, the decision to discontinue RoActemra for a laboratory abnormality should be based on the medical assessment of the individual patient.

#### General considerations for administration

RoActemra concentrate for intravenous (IV) infusion should be diluted by a healthcare professional using aseptic technique.

#### For patients $< 30$ kg

- From a 50 ml infusion bag, withdraw a volume of 0.9% (9 mg/ml) sterile, non-pyrogenic sodium chloride solution for injection equal to the volume of RoActemra concentrate required for the patient's dose
- The required amount of RoActemra concentrate (0.5 ml/kg) should be withdrawn from the vial and placed in the 50 ml infusion bag. This should be a final volume of 50 ml

#### For patients $\geq 30$ kg

- From a 100 ml infusion bag, withdraw a volume of 0.9% (9 mg/ml) sterile, non-pyrogenic sodium chloride solution for injection equal to the volume of RoActemra concentrate required for the patient's dose.

- The required amount of RoActemra concentrate (0.4 ml/kg) should be withdrawn from the vial and placed in the 100 ml infusion bag. This should be a final volume of 100 ml
- Slowly add RoActemra concentrate for IV infusion from each vial into the infusion bag. To mix the solution, gently invert the bag to avoid foaming
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted
- After dilution, the prepared solution for infusion is physically and chemically stable in sodium chloride 9 mg/ml (0.9%) at 30°C for 24 hours. From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in use storage times and conditions are the responsibility of the user and would normally be no longer than 24 hours at 2–8°C, unless dilution has taken place in controlled and validated aseptic conditions. RoActemra solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used
- Allow the fully diluted RoActemra solution to reach room temperature prior to infusion
- The infusion should be administered over 60 minutes and must be administered with an infusion set. Do not administer as an IV push or bolus
- RoActemra should not be infused concomitantly in the same IV line with other drugs. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of RoActemra with other medications

## RoActemra SC in pJIA



Do not use RoActemra SC for IV infusions. The recommended dose of Roactemra SC in pJIA patients is 162 mg given once every 2 weeks in patients weighing  $\geq 30$  kg, or once every 3 weeks in patients weighing  $< 30$  kg. A change in dose should only be based on a consistent change in the patient's body weight over time.

- RoActemra can be given as monotherapy (in case of intolerance to MTX or where continued treatment with MTX is inappropriate) or in combination with MTX
- There is no experience of the use of RoActemra with TNF antagonists or other biological treatments for pJIA patients. RoActemra is not recommended for use with other biological agents

### General dose advice

- Dose interruptions of RoActemra for laboratory abnormalities are recommended
- Reduction of RoActemra dose due to laboratory abnormalities has not been studied in pJIA
  - If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and RoActemra dosing interrupted until the clinical situation has been evaluated
- As there are many co-morbid conditions that may affect laboratory values in pJIA, the decision to discontinue RoActemra for a laboratory abnormality should be based on the medical assessment of the individual patient

### General considerations for administration

- RoActemra 162 mg is supplied in 0.9 ml of solution for injection as a pack of 4 single use pre-filled syringes. The following should be considered before administration:
- The pre-filled syringes should be stored at 2°C–8°C and should not be frozen
- The pre-filled syringes should be kept in the outer carton to protect them from light and should be kept dry. The pre-filled syringes should be kept out of sight and reach of children
- Inspect the pre-filled syringe visually for particulate matter and discolouration prior to administration. Do not use if the medicine is cloudy or contains particles, is any colour besides colourless to slightly yellowish, or if any part of the pre-filled syringe appears to be damaged
- Once removed from the refrigerator, RoActemra 162 mg/0.9 ml must be administered within 8 hours and should not be kept above 30°C
- After removing the pre-filled syringe from the refrigerator:
- The pre-filled syringe should be allowed to reach room temperature (18°C to 28°C) by waiting for 25 to 30 minutes, before injecting RoActemra 162 mg/0.9 ml. Do not warm up the pre-filled syringe in any other way

- After removing the needle-cap, the injection must be started within 5 minutes to prevent the medicine from drying out and blocking the needle. If the pre-filled syringe is not used within 5 minutes of removing the cap, you must dispose of it in a puncture-resistant container and use a new pre-filled syringe. Never re-attach the needle-cap after removal
- The pre-filled syringe should not be shaken
- If following insertion of the needle you cannot depress the plunger, you must dispose of the pre-filled syringe in a puncture-resistant container and use a new pre-filled syringe.
- The first dose should be administered by a healthcare professional and after proper training in injection technique, parents/guardians of pJIA patients may inject the pJIA patient with RoActemra if it is deemed appropriate
- Any unused product or waste material should be disposed of in accordance with local requirements.

For further information, please consult the Step by Step Dosing and Administration Guide.

## Switching from RoActemra IV to RoActemra SC

- Patients transitioning from IV to SC formulation should administer their first SC dose instead of the next scheduled IV dose under the supervision of a qualified healthcare professional.
- After proper training in injection technique, patients may be injected by a parent or guardian/caregiver.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Reporting forms and information can be found at [www.medicinesauthority.gov.mt/adrportal](http://www.medicinesauthority.gov.mt/adrportal). Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing [welwyn.uk\\_dsc@roche.com](mailto:welwyn.uk_dsc@roche.com) or calling +44(0)1707 367554.

As RoActemra is a biological medicine, healthcare professionals should report adverse reactions by brand name and batch number.





