RoActemra® (tocilizumab) for Rheumatoid Arthritis

IMPORTANT EFFICACY AND SAFETY INFORMATION

To assist healthcare professionals in assessing the benefits and risks associated with RoActemra therapy in patients with rheumatoid arthritis

Indications and usage for Rheumatoid Arthritis

RoActemra, in combination with methotrexate (MTX), is indicated for the treatment of moderate-to-severe active rheumatoid arthritis (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.

The efficacy of intravenously (IV) administered RoActemra in alleviating the signs and symptoms of RA was assessed in the Phase III development programme in five randomised, double-blind, multi-centre studies. Studies I–V enrolled patients ≥18 years of age with active RA diagnosed according to the American College of Rheumatology (ACR) criteria and who had at least eight tender and six swollen joints at baseline. Study II examined the efficacy of RoActemra on the rate of progression of joint damage and improvement of physical function in RA patients.

Patient counselling information and laboratory monitoring

Patient counselling information

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 that RoActemra may lower their resistance to infections.

Instruct the patient 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 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. 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 during treatment with RoActemra.

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

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

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 permanently discontinued.

- Gastrointestinal side effects:

Inform 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.

- Before you administer RoActemra, ask the patient if they:
  - Have an infection, are being treated for an infection or have a history of recurring infections
  - Have signs of an infection, such as a fever, cough or headache, or are feeling unwell
  - Have herpes zoster or any other skin infection with open sores
  - Have had any allergic reactions to previous medications, including RoActemra
  - Are pregnant, might be pregnant, intend to become pregnant, or are breast-feeding
  - Have diabetes or other underlying conditions that may predispose him or her to infection
  - Have tuberculosis (TB), or have 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 RoActemra therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating RoActemra

— Are taking other biological drugs to treat RA, or receiving atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin or benzodiazepines

— Have had or currently have viral hepatitis or any another hepatic disease

— Have a history of gastrointestinal ulcers or diverticulitis

— Have recently received a vaccination or are scheduled for any vaccination

— Have cancer, cardiovascular risk factors such as raised blood pressure and raised cholesterol levels, or moderate to severe kidney function problems

Laboratory monitoring

Neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. Lipids should be monitored 4 to 8 weeks following initiation of RoActemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

Clinical response

The potential benefits associated with RoActemra treatment

The percentages of patients achieving ACR20, ACR50 and ACR70 are shown below. In all studies, patients treated with 8 mg/kg RoActemra had statistically significant ACR20, ACR50 and ACR70 response rates versus MTX- or placebo-treated patients at Week 24. Some patients experienced ACR20 responses as early as 2 weeks for the RoActemra doses studied.

ACR responses in placebo-/MTX-/DMARD-controlled studies (percentage of patients)

	Study I AMBITION		Study II LITHE		Study III OPTION		Study IV TOWARD		Study V RADIATE	
Week	TCZ 8 mg/kg	MTX	TCZ 8 mg/kg + MTX	Placebo + MTX	TCZ 8 mg/kg + MTX	Placebo + MTX	TCZ 8 mg/kg + DMARD	Placebo + DMARD	TCZ 8 mg/kg + MTX	Placebo + MTX
	n=286	n=284	n=398	n=393	n=205	n=204	n=803	n=413	n=170	n=158
					ACR 20					
24	70%***	52%	56%***	27%	59%***	26%	61%***	24%	50%***	10%
52			56%***	25%						
					ACR 50					
24	44%**	33%	32%***	10%	44%***	11%	38%***	9%	29%***	4%
52			36%***	10%						
					ACR 70					
24	28%**	15%	13%***	2%	22%***	2%	21%***	3%	12%**	1%
52			20%***	4%						

TCZ – Tocilizumab
MTX – Methotrexate
DMARD – Disease-modifying anti-rheumatic drug
** $p<0.01$, TCZ vs. Placebo + MTX/DMARD
*** $p<0.0001$, TCZ vs. Placebo + MTX/DMARD

Patients in Studies I to V had a mean Disease Activity Score (DAS28) of 6.5 to 6.8 at baseline. Significant reductions in DAS28 from baseline (mean improvement) of 3.1 to 3.4 were observed in RoActemra-treated patients compared with control patients (1.3–2.1). The proportion of patients achieving a DAS28 clinical remission (DAS28 <2.6) was significantly higher in patients receiving RoActemra (28% to 34%) compared with 1% to 12% of control patients at 24 weeks. In Study II, 65% of patients achieved a DAS28 <2.6 at 104 weeks compared with 48% at 52 weeks and 33% at Week 24.

Phase IV study - Tocilizumab versus adalimumab in monotherapy

A 24-week double-blinded study that compared tocilizumab monotherapy with adalimumab monotherapy, evaluated 326 patients with RA who were intolerant of MTX or where continued treatment with MTX was considered inappropriate (including MTX inadequate responders). Patients in the tocilizumab arm received an intravenous (IV) infusion of tocilizumab (8mg/kg) every 4 weeks (q4w) and a subcutaneous (SC) placebo injection every 2 weeks (q2w). Patients in the adalimumab arm received an adalimumab SC injection (40 mg) q2w plus an IV placebo infusion q4w.

A statistically significant superior treatment effect was seen in favour of tocilizumab over adalimumab in control of disease activity from baseline to week 24 for the primary endpoint of change in DAS28 and for all secondary endpoints (Table below).

Efficacy results favouring tocilizumab monotherapy versus adalimumab monotherapy

	ADA + Placebo (IV) n = 162	TCZ + Placebo (SC) n = 163	*p*-value[a]
Primary Endpoint - Mean Change from baseline at Week 24			
DAS28 (adjusted mean)	–1.8	–3.3	
Difference in adjusted mean (95% CI)	–1.5 (–1.8, –1.1)		<0.0001
Secondary Endpoints - Percentage of Responders at Week 24[b]			
DAS28 <2.6, n (%)	17 (10.5)	65 (39.9)	<0.0001
DAS28 ≤3.2, n (%)	32 (19.8)	84 (51.5)	<0.0001
ACR20 response, n (%)	80 (49.4)	106 (65.0)	0.0038
ACR50 response, n (%)	45 (27.8)	77 (47.2)	0.0002
ACR70 response, n (%)	29 (17.9)	53 (32.5)	0.0023

[a] *p*-value is adjusted for region and duration of RA for all endpoints and additionally baseline value for all continuous endpoints.
[b] Non-responder imputation used for missing data. Multiplicity controlled using Bonferroni-Holm Procedure

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 biological treatments for moderate-to-severe RA 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 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 biologic therapies in RA, 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 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 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 infusion of RoActemra. Such reactions may be more severe, and potentially fatal, in patients who have experienced hypersensitivity reactions during previous infusions 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 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 8mg/kg + MTX. 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 x 10^9/l. In patients who develop an ANC <0.5 x 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. There has been no clear association between decreases in neutrophils and the occurence of serious infections in clinical trials with RoActemra to date.

Neutrophils should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice.

Low absolute neutrophil count (ANC)

Laboratory value (cells x 10^9/l)	Action
ANC >1	Maintain RoActemra dose
ANC 0.5 to 1	Interrupt RoActemra dosing When ANC increases >1 x 10^9/l resume RoActemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
ANC <0.5	Discontinue RoActemra

- Platelets

Decreases in platelet counts have occurred following treatment with RoActemra 8 mg/kg plus MTX.

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 a platelet count <50 x 10^3/µl, continued treatment is not recommended.

Platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice.

Low platelet count

Laboratory value (cells x 10^3/µl)	Action
50 to 100	Interrupt RoActemra dosing When platelet count >100 x 10^3/µl resume RoActemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
<50	Discontinue RoActemra

- 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 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 confirmed by repeat testing, RoActemra treatment should be interrupted.

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, reduce RoActemra dose to 4 mg/kg or interrupt RoActemra until ALT or AST have normalised
>3 to 5 x ULN	Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate Interrupt RoActemra dosing until <3 x ULN and follow recommendations above for >1 to 3 x ULN For persistent increases >3 x ULN (confirmed by repeat testing), discontinue RoActemra
>5 x ULN	Discontinue RoActemra

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

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

The risk of malignancy is increased in patients with RA. 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 all 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 RA patients

RA patients have an increased risk for cardiovascular disorders and should have risk factors (e.g., hypertension, hyperlipidaemia) managed as part of usual standard of care.

Renal impairment

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

Undesirable effects

The most commonly reported adverse drug reactions (ADRs) (occurring in ≥5% of patients treated with RoActemra monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

- Infections

In the 6-month controlled studies (studies I-V), the rate of all infections reported with RoActemra 8 mg/kg plus DMARD treatment was 127 events per 100 patient-years compared with 112 events per 100 patient-years in the placebo plus DMARD group. In the long-term exposure population, the overall rate of infections with RoActemra was 108 events per 100 patient-years exposure.

In 6-month controlled clinical studies (studies I-V), the rate of serious infections with RoActemra 8 mg/kg plus DMARDs was 5.3 events per 100 patient-years exposure compared with 3.9 events per 100 patient-years exposure in the placebo plus DMARD group. In the monotherapy study the rate of serious infections was 3.6 events per 100 patient-years of exposure in the RoActemra group and 1.5 events per 100 patient-years of exposure in the MTX group.

In the long-term exposure population, the overall rate of serious infections (bacterial, viral and fungal) was 4.7 events per 100 patient-years. Reported serious infections, some with fatal outcome, included active tuberculosis, which may present with intrapulmonary or extrapulmonary disease, invasive pulmonary infections, including candidiasis, aspergillosis, coccidioidomycosis and pneumocystis jirovecii, pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported.

Other adverse reactions

Summary of ADRs occurring in patients with RA receiving RoActemra treatment as monotherapy or in combination with MTX or other DMARDs in the double-blind controlled period

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Infections and infestations	Upper respiratory tract infections	Cellulitis, Pneumonia, Oral herpes simplex, Herpes zoster	Diverticulitis
Gastrointestinal disorders		Abdominal pain, Mouth ulceration, Gastritis	Stomatitis, Gastric ulcer
Skin and subcutaneous tissue disorders		Rash, Pruritus, Urticaria	
Nervous system disorders		Headache, Dizziness	
Investigations		Hepatic transaminases increased, Weight increased, Total bilirubin increased*	
Vascular disorders		Hypertension	
Blood and lymphatic system disorders		Leukopenia, Neutropenia	
Metabolism and nutrition disorders	Hypercholesterolaemia*		Hypertriglyceridaemia
General disorders and administration site conditions		Peripheral oedema, Hypersensitivity reactions	
Eye disorders		Conjunctivitis	
Respiratory, thoracic and mediastinal disorders		Cough, Dyspnoea	
Renal disorders			Nephrolithiasis
Endocrine disorders			Hypothyroidism

* Includes elevations collected as part of routine laboratory monitoring

Infusion reactions

In the 24 week controlled trials, adverse events associated with infusion (selected events occurring during or within 24 hours of infusion) were reported by 6.9% of patients in the RoActemra 8 mg/kg plus DMARD group and 5.1% of patients in the placebo plus DMARD group. Events reported during the infusion were primarily episodes of hypertension; events reported within 24 hours of finishing an infusion were headache and skin reactions (rash, urticaria). These events were not treatment limiting.

The rate of anaphylactic reactions, occurring in a total of 6 out of 3,778 patients (0.2%), was several-fold higher with the 4 mg/kg dose, compared to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with RoActemra and requiring treatment discontinuation were reported in a total of 13 out of 3,778 patients (0.3%) treated with RoActemra during the controlled and open-label clinical studies. These reactions were generally observed during the second to fifth infusions of RoActemra. Fatal anaphylaxis has been reported after marketing authorisation during treatment with RoActemra.

Interstitial lung disease

Impaired lung function may increase the risk for developing infections. There have been post-marketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Immunogenicity

A total of 2,876 patients have been tested for anti-RoActemra antibodies in the 6-month controlled clinical trials. Of the 46 patients (1.6%) who developed anti-RoActemra antibodies, 6 had an associated medically significant hypersensitivity reaction, of which 5 led to permanent discontinuation of treatment. Thirty patients (1.1%) developed neutralising antibodies.

Malignancies

The risk of malignancy is increased in patients with RA. Immunomodulatory medicinal products may increase the risk of malignancy. The clinical data are insufficient to assess the potential incidence of malignancy following exposure to tocilizumab. Long term safety evaluations are ongoing.

Drug interactions

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 RA. 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.

In a study in RA patients, levels of simvastatin (CYP3A4) were decreased by 57% one week following a single dose of RoActemra, to the level similar to, or slightly higher than, those observed in healthy subjects.

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, 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

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.

Elderly patients

No dose adjustment is required in patients aged 65 years and older.

Renal impairment

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

Hepatic impairment

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

Dosage and administration

The recommended dose of RoActemra for adult patients with RA is 8 mg/kg body weight, but no higher than 800 mg, given every 4 weeks as a 1-hour, IV infusion.

- RoActemra can be used concomitantly with MTX or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate
- RoActemra has not been studied in combination with TNF antagonists or other biologic treatments for RA. RoActemra is not recommended for use with other biologic agents

General dose advice

- It is not recommended to initiate RoActemra treatment in patients with a low neutrophil count, i.e., absolute neutrophil count (ANC) less than 2 x 10^9/l. In patients who develop an ANC <0.5 x 10^9/l, continued treatment is not recommended
- 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 a platelet count <50 x 10^3/µl, continued treatment is not recommended
- 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. For ALT or AST elevations >3 to 5 x ULN, confirmed by repeat testing, RoActemra treatment should be interrupted until <3 x ULN
- Reduction of dose from 8 mg/kg to 4 mg/kg is recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropaenia and thrombocytopaenia

General considerations for administration

RoActemra concentrate for intravenous (IV) infusion should be diluted to 100 ml by a healthcare professional using aseptic technique.

- 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 solution required for the patient's dose. The expiry date should always be checked before use
- 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

- RoActemra should be refrigerated for storage and the fully diluted RoActemra solution should be allowed to reach room temperature before it is infused. The fully diluted RoActemra solutions for infusion should be used immediately. If not used immediately it may be stored at 2–8°C or room temperature (if diluted under controlled and validated aseptic conditions) for up to 24 hours and should be protected from light. 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

If you have any further questions relating to RoActemra please contact Roche Medical Information on +44 (0)800 3281629 or email: medinfo.uk@roche.com.

Suspected adverse reactions associated with the use of RoActemra should be reported to: Medicines Authority Post-licensing Directorate 203. Level 3. Rue D'Argens, Gzira GZR 1368, or at: http://www.medicinesauthority.gov.mt/adrportal. Suspected adverse events should also be reported to Roche by phone on +44 (0)1707 367554, fax on +44 (0)1707 367582 or e-mail at welwyn.uk_dsc@roche.com.

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