STEP BY STEP INFUSION INSTRUCTIONS FOR *RoACTEMRA® (tocilizumab)*

RoACTEMRA®
tocilizumab

For further information, please refer to RoACTEMRA® (tocilizumab) Summary of Product Characteristics

Prescribing information can be found on the inside back cover.

Roche

Date of preparation: July 2012 RCUKACTE00628

Quick Reference Guide

1. Go through the pre-administration checklist with your patient, determine his or her infection risk and history

2. Take baseline assessments to ensure the patient is healthy enough to receive the infusion

3. Weigh the patient and calculate the RoACTEMRA dose required using the dose calculation table

4. Gather all supplies necessary for RoACTEMRA infusion

5. Prepare the patient for the infusion of RoACTEMRA by answering any questions he or she might have and preparing the infusion set and intravenous site

6. Prepare the RoACTEMRA infusion by diluting to 100 ml using aseptic technique

7. Begin the RoACTEMRA infusion, administered over 1 hour using an infusion set

This booklet will guide you through the RoACTEMRA infusion process in 7 steps.

Before therapy begins

Prior to each infusion, it is important that you review step 1 (Pre-administration Checklist) in this booklet with your patient and allow ample time to discuss any questions he or she may have.

Blood tests will need to be carried out according to the following schedule:

Monitor alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. When clinically indicated, other liver function tests including bilirubin should be considered.

Monitor neutrophils and platelets 4–8 weeks after start of therapy and thereafter according to standard clinical practice. 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.

Assess lipid parameters 4–8 weeks after start of therapy and manage according to local guidelines.

See Healthcare Professional brochure entitled '*Important Efficacy and Safety Information*' for further information.

RoACTEMRA patient brochures and other information can be requested from your sales representative. If you have any further questions, please email the Roche Medical Information helpline on **medinfo.uk@roche.com** or phone **+44 800 328 1629**.

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1 Pre-administration Checklist

You may need to test the patient's blood for one or more of the following prior to infusion: neutrophils, platelets, liver enzymes and cholesterol.

Before beginning RoACTEMRA therapy, discuss with the patient whether he or she:

- Is taking other medicines. This includes prescription and non-prescription drugs, statins[1], vitamins and herbals
- Is taking any other drugs to treat rheumatoid arthritis such as methotrexate (MTX), etanercept, adalimumab, infliximab, rituximab, abatacept, anakinra, golimumab and certolizumab
- Is pregnant, planning a pregnancy, or breastfeeding
- Has hypersensitivity to the active substance or to any of the excipients of RoACTEMRA
- Has an infection or is being treated for an infection
- Has signs of an infection, such as a fever, cough, or headache, or feeling unwell
- Has skin infections with open sores
- Gets a lot of infections
- Has diabetes or other conditions that increase the chance for infections e.g. interstitial lung disease
- Has tuberculosis (TB), or has been in close contact with someone who has had TB. The patient should be tested for TB before beginning RoACTEMRA therapy
- Has symptoms that may be due to complicated diverticulitis, such as abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever
- Has active hepatic disease or hepatic impairment, or is taking potentially hepatotoxic drugs (e.g. MTX)
- Has a low neutrophil or platelet count[2]
- Treatment is not recommended for patients with an absolute neutrophil count (ANC) below 2 x 10^9/L
- Has recently received, or may in the future receive, live or live-attenuated vaccine
- Has symptoms that may be due to a central demyelinating disorder
- Has risk factors for cardiovascular disorders (e.g. hyperlipidaemia)
- Is on a controlled sodium diet

See the Healthcare Professional brochure entitled '*Important Efficacy and Safety Information*' for further information and treatment recommendations in case of abnormal laboratory parameters.

Discuss with the patient any questions that he or she may have about this information.

1. When starting or stopping therapy with RoACTEMRA, patients taking medicinal products which are individually adjusted and are metabolised via CYP450 3A4, 1A2 or 2C9 (eg. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses may need to be increased to maintain therapeutic effect. Given its long elimination half-life ($t_{½}$), the effect of RoACTEMRA on CYP450 enzyme activity may persist for several weeks after stopping therapy.
2. If the patient has a low neutrophil or platelet count or raised liver enzymes the dosing of RoACTEMRA may need to be interrupted or the dose reduced. Increases in lipid parameters require management according to local guidelines.

2 *Take baseline assessments*

Take baseline assessments to ensure the patient is healthy enough to receive the infusion. Vital signs may include:

- Blood pressure
- Temperature
- Pulse

3 *Weigh patient and calculate RoACTEMRA dose*

RoACTEMRA dosing is calculated based on each patient's weight. Use the calculation provided on the next page, or locate the patient's weight on the chart to find the corresponding dose.

If the patient's dose has been calculated prior to the infusion date, take his or her weight to make sure it has not changed from the time of the original calculation to require a change in dose. If the patient's weight has changed, then a dosing adjustment will be necessary. Refer to the chart to check whether a dosing adjustment is necessary.

RoACTEMRA dosing in patients with body weight over 100 kg
For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended.
Doses above 1.2 g have not been evaluated in clinical studies.

RoACTEMRA dosing can be calculated based on each patient's weight:

For 8 mg/kg the dose calculation is as follows

Patient weight (kg) X 8 mg = RoACTEMRA dose

Once the dose is calculated, choose the vial combination of RoACTEMRA that best matches the patient's needs. RoACTEMRA is available in 3 different dosing volumes:

400 mg (20 ml) 200 mg (10 ml) 80 mg (4 ml)

8 mg/kg dose

Weight (kg)	Weight (lbs)	Dose (mg)	Dose (ml)	Vial combinations
50	110	400	20.0	400 mg
51	112.2	408	20.4	200 mg + 200 mg + 2 × 80 mg
52	114.4	416	20.8	200 mg + 200 mg + 2 × 80 mg
53	116.6	424	21.2	200 mg + 200 mg + 2 × 80 mg
54	118.8	432	21.6	200 mg + 200 mg + 2 × 80 mg
55	121	440	22.0	200 mg + 200 mg + 2 × 80 mg
56	123.2	448	22.4	400 mg + 80 mg
57	125.4	456	22.8	400 mg + 80 mg
58	127.6	464	23.2	400 mg + 80 mg
59	129.8	472	23.6	400 mg + 80 mg
60	132	480	24.0	400 mg + 80 mg
61	134.2	488	24.4	200 mg + 200 mg + 2 × 80 mg + 80 mg
62	136.4	496	24.8	200 mg + 200 mg + 2 × 80 mg + 80 mg
63	138.6	504	25.2	200 mg + 200 mg + 2 × 80 mg + 80 mg
64	140.8	512	25.6	200 mg + 200 mg + 2 × 80 mg + 80 mg
65	143	520	26.0	200 mg + 200 mg + 2 × 80 mg + 80 mg
66	145.2	528	26.4	400 mg + 2 × 80 mg
67	147.4	536	26.8	400 mg + 2 × 80 mg
68	149.6	544	27.2	400 mg + 2 × 80 mg
69	151.8	552	27.6	400 mg + 2 × 80 mg
70	154	560	28.0	400 mg + 2 × 80 mg
71	156.2	568	28.4	400 mg + 200 mg
72	158.4	576	28.8	400 mg + 200 mg
73	160.6	584	29.2	400 mg + 200 mg
74	162.8	592	29.6	400 mg + 200 mg
75	165	600	30.0	400 mg + 200 mg

8 mg/kg dose

Weight (kg)	Weight (lbs)	Dose (mg)	Dose (ml)	Vial combinations
76	167.2	608	30.4	400 mg + 2 × 80 mg + 2 × 80 mg
77	169.4	616	30.8	400 mg + 2 × 80 mg + 2 × 80 mg
78	171.6	624	31.2	400 mg + 2 × 80 mg + 2 × 80 mg
79	173.8	632	31.6	400 mg + 2 × 80 mg + 2 × 80 mg
80	176	640	32.0	400 mg + 2 × 80 mg + 2 × 80 mg
81	178.2	648	32.4	400 mg + 200 mg + 80 mg
82	180.4	656	32.8	400 mg + 200 mg + 80 mg
83	182.6	664	33.2	400 mg + 200 mg + 80 mg
84	184.8	672	33.6	400 mg + 200 mg + 80 mg
85	187	680	34.0	400 mg + 200 mg + 80 mg
86	189.2	688	34.4	400 mg + 2 × 80 mg + 2 × 80 mg + 80 mg
87	191.4	696	34.8	400 mg + 2 × 80 mg + 2 × 80 mg + 80 mg
88	193.6	704	35.2	400 mg + 2 × 80 mg + 2 × 80 mg + 80 mg
89	195.8	712	35.6	400 mg + 2 × 80 mg + 2 × 80 mg + 80 mg
90	198	720	36.0	400 mg + 2 × 80 mg + 2 × 80 mg + 80 mg
91	200.2	728	36.4	400 mg + 200 mg + 2 × 80 mg + 80 mg
92	202.4	736	36.8	400 mg + 200 mg + 2 × 80 mg + 80 mg
93	204.6	744	37.2	400 mg + 200 mg + 2 × 80 mg + 80 mg
94	206.8	752	37.6	400 mg + 200 mg + 2 × 80 mg + 80 mg
95	209	760	38.0	400 mg + 200 mg + 2 × 80 mg + 80 mg
96	211.2	768	38.4	400 mg + 400 mg
97	213.4	776	38.8	400 mg + 400 mg
98	215.6	784	39.2	400 mg + 400 mg
99	217.8	792	39.6	400 mg + 400 mg
≥100	≥220	800	40.0	400 mg + 400 mg

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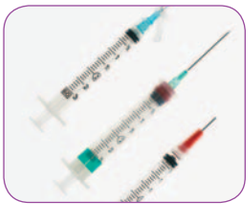
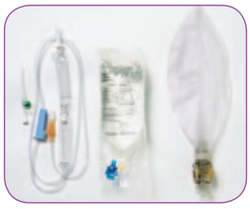
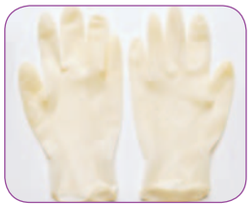
4 Gather all necessary supplies

You will need:

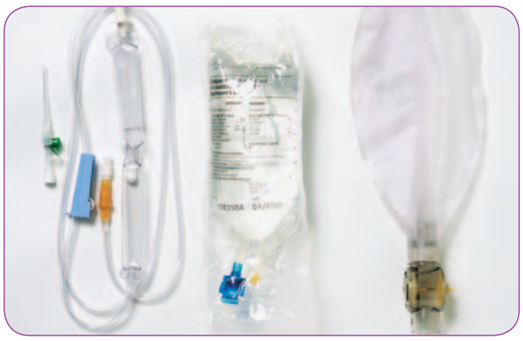
- RoACTEMRA, at room temperature
- Syringes and large-bore needles
- One primary infusion set with Y site
- One 100 ml bag of 0.9% (9 mg/ml) sodium chloride
- One intravenous (IV) catheter
- Medicines to manage an infusion-related anaphylactic reaction
- Gauze
- Tourniquet
- Gloves
- Alcohol/cleansing wipes




5 *Prepare the patient for the infusion*

- Review the *What You Should Know About RoACTEMRA* patient brochure with the patient and answer any questions he or she might have
- RoACTEMRA does not require premedication. Start the infusion of 0.9% (9 mg/ml) sodium chloride



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6 *Prepare the RoACTEMRA infusion*

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 drugs.

RoACTEMRA is a ready-mix solution and requires no reconstitution. RoACTEMRA concentrate for IV infusion should be diluted to 100 ml by a healthcare professional using aseptic technique as follows:

- Parenteral drug 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
- Although RoACTEMRA should be refrigerated for storage, the fully diluted RoACTEMRA solution should be allowed to reach room temperature before it is infused. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2–8°C, unless dilution has taken place in controlled and validated aseptic conditions. Keep the vial(s) in the outer carton in order to protect from light. RoACTEMRA solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used
- From a 100 ml infusion bag, withdraw a volume of sterile non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection, equal to the volume of RoACTEMRA concentrate required for the patient's dose, under aseptic conditions.
- Slowly add the required amount of RoACTEMRA concentrate (0.4 ml/kg) for IV infusion from each vial into the infusion bag. To mix the solution, gently invert the bag to avoid foaming
- Dispose of needle and syringe in sharps containers when finished

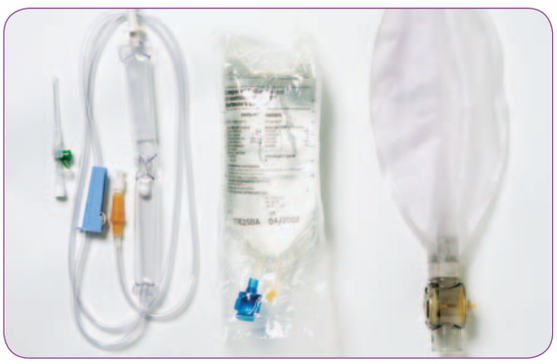
7 *Begin the RoACTEMRA infusion*

The infusion should be administered over 1 hour. **It must be administered with an infusion set and should never be administered as an IV push or bolus.**

Prior to the infusion, inform the patient of potential hypersensitivity reactions. Most reactions happen during infusion or within 24 hours after infusion. They can range from mild to severe. 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.

- Mild to moderate reactions include:
  - —Hypertension
  - —Headache
  - —Skin reactions, such as rash, pruritus and urticaria
- Severe reactions include:
  - —Anaphylaxis

During the infusion, watch the patient closely for any hypersensitivity reaction. 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.



Once the infusion is completed, remove the catheter and dispose of all supplies properly, clean the infusion site and check the patient's vital signs.

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FREQUENTLY ASKED QUESTIONS

How do I store RoACTEMRA vials?

RoACTEMRA must be refrigerated at 2°C–8°C. Do not freeze. Protect the vials from light by storage in the original package until time of use.

What vial sizes are available, and which should we stock?

RoACTEMRA is available in 3 different dosing vials: 400 mg (20 ml), 200 mg (10 ml) and 80 mg (4 ml). As the dosing of RoACTEMRA is calculated based upon patient weight, you may need a supply of all 3 dosing vials on hand in order to select the correct vial combination for each patient.

Do I need to administer premedication?

No premedication is required before administering RoACTEMRA.

How do I prepare RoACTEMRA for infusion? What diluents can I use?

RoACTEMRA concentrate for IV infusion should be diluted to 100 ml with 0.9% (9 mg/ml) sodium chloride solution for injection using aseptic technique as follows:

- Parenteral drug 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
- From a 100 ml infusion bag, withdraw a volume of sterile non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection, equal to the volume of RoACTEMRA concentrate required for the patient's dose, under aseptic conditions
- 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
- Although RoACTEMRA should be refrigerated for storage, the fully diluted RoACTEMRA solution should be allowed to reach room temperature before it is infused
- Dispose of needle and syringe in sharps containers when finished

What is the infusion duration?

RoACTEMRA is administered over a 1 hour period. It must be administered with an infusion set and should never be administered as an IV push or bolus.

How do I store the diluted infusion? What is the stability of RoACTEMRA?

The fully diluted RoACTEMRA solutions for infusion may be stored at 2°C–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. After dilution, the prepared solution for infusion is physically and chemically stable at 30°C for 24 hours. The prepared solution for infusion should be used immediately. If not, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C–8°C, unless dilution has taken place in controlled and validated aseptic conditions.

What should I look for during the infusion?

Watch the patient closely for any hypersensitivity, including anaphylaxis. Most reactions happen during infusion or within 24 hours after infusion. They can range from mild to severe. 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

- Mild to moderate reactions include:
  - —Hypertension
  - —Headache
  - —Skin reactions, such as rash, pruritus and urticaria
- Severe reactions include:
  - —Anaphylaxis

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.

What kinds of side effects and reactions can occur during or after the infusion, and how common are they?

The most common side effects with RoACTEMRA are upper respiratory tract infections (common cold, sinus infection), headache, temporary increases in blood pressure, rash and dizziness.

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.

How frequently should I monitor the patient's vital signs?

Take the patient's vital signs before and after each infusion.

What if a patient cannot schedule his or her infusion in exactly 4 weeks?

RoACTEMRA should be administered once every 4 weeks. Contact the prescriber for any deviations from that schedule.

What information do I need to provide to the patient about RoACTEMRA?

Before beginning RoACTEMRA therapy, it is important that you review the *What You Should Know About RoACTEMRA patient brochure* with each patient. This educational tool contains valuable information that will help your patients fully understand what they may expect from their treatment.

Prior to each infusion, it is important that you review the Pre-administration Checklist included in this document. The patient should be allowed ample time to review and discuss any questions he or she may have.

To request further information about RoACTEMRA, please call Medical Information on +44 800 328 1629.

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PRESCRIBING INFORMATION RoActemra®

Please refer to RoActemra SPC for full prescribing information.

Indications: Rheumatoid Arthritis (RA): 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. **Systemic juvenile idiopathic arthritis (sJIA):** Indicated for the treatment of active sJIA in patients ≥ 2 years of age, 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.

Dosage and Administration: Patients should be given the Patient Alert Card. **RA:** 8 mg/kg iv infusion given once every 4 weeks. Doses exceeding 800 mg per infusion are not recommended. **sJIA:** 8 mg/kg for patients weighing ≥ 30 kg or 12 mg/kg for patients weighing < 30 kg, given as iv infusion every 2 weeks.

Dose adjustments: RA: Dose reduction to 4 mg/kg, or interruptions, are recommended in the event of raised liver enzymes, low absolute neutrophil count (ANC) or low platelet count. RoActemra should not be initiated in patients with ANC count below 2 x 10^9/l. **sJIA:** Interrupt treatment in the event of raised liver enzymes, low ANC or low platelet count; dose reductions have not been studied in these patients.

Contraindications: Hypersensitivity to any component of the product; active, severe infections.

Precautions: Both indications: *Infections:* Cases of serious and sometimes fatal infections have been reported; interrupt therapy until controlled. Caution in patients with recurring/chronic infections, or other conditions which may predispose to infection. *Tuberculosis:* Screen for and treat latent TB prior to starting therapy. *Hypersensitivity reactions:* Serious hypersensitivity reactions have been reported and may be more severe and potentially fatal in patients who have experienced hypersensitivity reactions with previous infusions even if they have received premedication with steroids and antihistamines. Appropriate treatment should be available for immediate use if anaphylaxis occurs. If an anaphylactic reaction or other serious hypersensitivity/serious infusion related reaction occurs, permanently discontinue RoActemra. *Hepatic disease/impairment:* Use with caution in patients with active hepatic disease/impairment. *Transaminase elevations:* Not recommended in patients with ALT or AST > 5 x ULN; caution in patients with ALT or AST > 1.5 x ULN. *Haematological abnormalities:* Caution in patients with platelet count < 100 x 10^3/µl. Continued treatment not recommended in patients with ANC < 0.5 x 10^9/l or platelet count < 50 x 10^3/µl. *Lipid parameters:* If elevated, follow local guidelines for managing hyperlipidaemia. *Vaccinations:* Live and live attenuated vaccines should not be given concurrently. *Combined with other biologic treatments:* Not recommended. **RA only:** *Viral reactivation:* Has been reported with biologics. *Diverticulitis:* Caution in patients with a history of intestinal ulceration or diverticulitis. Patients with symptoms of complicated diverticulitis should be evaluated promptly.

sJIA only: Macrophage activation syndrome (MAS) is a serious life-threatening disorder which may develop in sJIA patients. Tocilizumab treatment has not been studied during active MAS.

Interactions: Patients taking other medicines which are metabolised via CYP450 3A4, 1A2, or 2C9 should be monitored as doses may need to be adjusted.

Pregnancy and Lactation: Women should use contraception during and for 3 months after treatment. A decision on whether to continue/discontinue breastfeeding on RoActemra therapy should take into account relative benefits to mother and child.

Undesirable effects: RA: *Very common ADRs (≥ 1/10):* URTI, hypercholesterolaemia. *Common ADRs (≥ 1/100 to < 1/10):* cellulitis, pneumonia, oral herpes simplex, herpes zoster, abdominal pain, mouth ulceration, gastritis, rash, pruritus, urticaria, headache, dizziness, increased hepatic transaminases, increased weight and increased total bilirubin, hypertension, leukopenia, neutropenia, peripheral oedema, hypersensitivity reactions, conjunctivitis, cough, dyspnoea. *Medically significant events: Infections:* Opportunistic and serious infections have been reported, some serious infections had a fatal outcome. Impaired lung function may increase the risk of developing infections. There have been post-marketing reports of interstitial lung disease, some of which had a fatal outcome. *GI perforations:* Primarily reported as complications of diverticulitis. *Infusion reactions:* Clinically significant hypersensitivity reactions requiring treatment discontinuation were reported and were generally observed during the 2nd–5th infusions. Fatal anaphylaxis has been reported. *Other:* Decreased neutrophil count, decreased platelet count, hepatic transaminase elevations, lipid parameter increases, very rare cases of pancytopenia. **sJIA:** In general ADRs similar in type to those in RA. *Medically significant events: Infections:* Serious infections were similar to those seen in RA, with additions of varicella and otitis media. *Infusion reactions:* A hypersensitivity reaction that resulted in treatment discontinuation occurred in one out of 112 patients (< 1%). *Other:* decreased neutrophil count, decreased platelet count, decreased IgG, hepatic transaminase elevations, lipid parameter increases. Consult SPC for other ADRs.

Legal category: POM. **Presentations and Basic NHS Costs:** 80 mg of tocilizumab in 4 ml (20 mg/ml) 1 vial: £102.40, 20 mg of tocilizumab in 10 ml (20 mg/ml) 1 vial: £256.00, 400 mg of tocilizumab in 20 ml (20 mg/ml) 1 vial: £512.00.

Marketing Authorisation Numbers: EU/1/08/492/01 (80 mg), EU/1/08/492/03 (200 mg), EU/1/08/492/05 (400 mg).

Marketing Authorisation Holder: Roche Registration Limited, 6 Falcon Way, Welwyn Garden City, Herts AL7 1TW. RoActemra is a registered trade mark.

Date of Preparation: June 2012. RCUKMEDI00010

Adverse events should be reported to Roche Products Limited. Please contact the Drug Safety Centre, Roche Products Limted, 6 Falcon Way, Shire Park, Welwyn Garden City, Hertfordshire, England. Telephone number +44 1707 367554. Adverse events may otherwise be reported via the national Adverse Drug Reactions (ADRs) reporting system. Reporting forms and information can be found at: http://medicinesauthority.gov.mt/phvigilance.htm

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