IMPORTANT EFFICACY AND SAFETY INFORMATION

to assist healthcare professionals in assessing the benefits and risks associated with RoACTEMRA® (tocilizumab) therapy

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tocilizumab

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

Prescribing information can be found on the back cover.

Roche

Date of preparation: July 2012 RCUKACTE00618

Contents

Indications and Usage

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 antirheumatic 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.

In the Phase III development programme, the efficacy of RoACTEMRA in alleviating the signs and symptoms of RA was assessed 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 8 tender and 6 swollen joints at baseline.

Patient Counselling Information and Laboratory Monitoring

Patient counselling information

Patients should be advised of the potential benefits and risks of RoACTEMRA.

- Infections:

Inform patients that RoACTEMRA may lower their resistance to infections. Instruct the patient on the importance of contacting their doctor immediately when symptoms suggesting infection appear in order to assure rapid evaluation and appropriate treatment.

- Gastrointestinal side effects:

Inform patients that some people who have been treated with RoACTEMRA have had serious side effects in the stomach and intestines. Instruct the patient about the importance of contacting their doctor immediately when symptoms of severe, persistent abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever appear, to assure rapid evaluation and appropriate treatment.

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Patient Counselling Information and Laboratory Monitoring (continued)

- Hypersensitivity reactions:

Inform patients about potential hypersensitivity reactions. Mild reactions were generally observed within 24 hours, while severe reactions were generally observed during the second to fifth infusion.

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

  — Severe reactions include:
    - Anaphylaxis

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.

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

…are pregnant or want to become pregnant, or are breastfeeding

…have diabetes or other underlying conditions that may predispose to infection

…have tuberculosis (TB), or have been in close contact with someone who has had TB

…are taking other biological drugs to treat RA, as well as atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin or benzodiazepines

…have had or now have viral hepatitis or any other hepatic disease

…have a history of gastrointestinal ulcers or diverticulitis

…have had or now have impaired lung function

…have recently received a vaccination or are scheduled for any vaccination

…are on a sodium restricted diet

…are known to be hypersensitive to RoACTEMRA or any of the excipients

…have haematological abnormalities

…have cancer

Laboratory monitoring

Alanine aminotransferase (ALT) and **aspartate aminotransferase** (AST) should be monitored 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.

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

Assessment of **lipid parameters** should be performed 4 to 8 weeks following initiation of treatment, and then managed according to local guidelines.

Please refer to SPC for further guidance on laboratory monitoring.

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Clinical Response

The percentages of patients achieving ACR 20, 50 and 70 responses are shown below. In all studies, patients treated with 8 mg/kg RoACTEMRA had statistically significantly higher ACR 20, 50 and 70 response rates versus MTX- or placebo-treated patients at Week 24. Some patients experienced ACR 20 responses as early as 2 weeks after treatment was initiated with RoACTEMRA.

ACR Responses in Placebo/MTX/DMARD Controlled Studies (Percent 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 – RoACTEMRA
MTX – Methotrexate
DMARD – Disease-modifying anti-rheumatic drug
* – $p < 0.05$, TCZ vs. placebo + MTX/DMARD
** – $p < 0.01$, TCZ vs. placebo + MTX/DMARD
*** – $p < 0.0001$, TCZ vs. placebo + MTX/DMARD

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 (eg, 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, 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 when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

Tuberculosis

As recommended for other biological treatments in RA, 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.

Viral reactivation

Viral reactivation (e.g. hepatitis B virus) has been reported with biologic therapies for rheumatoid arthritis. 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.

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 drugs may increase the risk of malignancy.

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Warnings and Precautions (continued)

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.

Cardiovascular risk in RA patients

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

Vaccinations

Live and live attenuated vaccines should not be given concurrently with RoACTEMRA as clinical safety has not been established.

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.

Combination with TNF antagonists

There is no experience with the use of RoACTEMRA with TNF antagonists or other biological treatments for RA. RoACTEMRA is not recommended for use with other biological agents.

Sodium

RoACTEMRA contains 1.17 mmol (or 26.55 mg) sodium per maximum dose of 1200 mg, which should be taken into consideration by patients on a controlled sodium diet. Doses below 1025 mg of this medicinal product contain less than 1 mmol sodium (23 mg), i.e. essentially ‘sodium free’.

Laboratory parameters

• Neutrophils

Decreases in neutrophil counts have occurred following treatment with RoACTEMRA 8 mg/kg in combination with MTX. There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist.

Severe neutropenia may be associated with an increased risk of serious infections, although there has been no clear association between decreases in neutrophils and the occurrence of serious infections in clinical trials with RoACTEMRA to date.

In patients not previously treated with RoACTEMRA, initiation is not recommended in patients with an ANC <2 x 10^9/L. In patients who develop an ANC <0.5 x 10^9/L continued treatment is not recommended.

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

Low absolute neutrophil count (ANC)

Lab value (cells x 10^9/L)	Action
ANC >1	Maintain dose
ANC 0.5 - 1	Interrupt RoACTEMRA dosing When ANC increases above 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 been observed following treatment with RoACTEMRA 8 mg/kg in combination with 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 4–8 weeks after start of therapy and thereafter according to standard clinical practice.

Low platelet count

Lab value (cells x 10^3/µL)	Action
50 - 100	Interrupt RoACTEMRA dosing When platelet count increases above 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 commonly reported with RoACTEMRA treatment, without progression to hepatic injury. An increased frequency of these elevations was observed when potentially hepatotoxic drugs (eg, MTX) were used in combination with RoACTEMRA.

Caution should be exercised when considering initiation of RoACTEMRA treatment in patients with elevated ALT or AST > 1.5 x 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 > 3–5 x ULN, confirmed by repeat testing, RoACTEMRA treatment should be interrupted. When clinically indicated, other liver function tests including bilirubin should be considered.

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Warnings and Precautions (continued)

Laboratory parameters

Liver enzyme abnormalities

Lab value	Action
>1 - 3 x ULN	Dose modify concomitant MTX if appropriate For persistent increases in this range, reduce dose of RoACTEMRA to 4 mg/kg or interrupt RoACTEMRA until ALT or AST have normalised Restart with 4 mg/kg or 8 mg/kg as clinically appropriate
>3 - 5 x ULN Confirmed by repeat testing	Interrupt RoACTEMRA dosing until <3 x ULN and follow recommendations above for >1 to 3 x ULN For persistent increases >3 x ULN, 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 4–8 weeks following initiation of RoACTEMRA therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

Adverse Drug Reactions

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, the rate of all infections reported with RoACTEMRA 8 mg/kg plus DMARD treatment was 127 events per 100 patient years compared to 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, the rate of serious infections with RoACTEMRA 8 mg/kg plus DMARDs was 5.3 events per 100 patient years exposure compared to 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 (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.

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Adverse Drug Reactions (continued)

Summary of ADRs occurring in patients with RA receiving RoACTEMRA treatment as monotherapy or in combination with MTX or other DMARDs

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	
Metabolic 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

Gastrointestinal Perforation

During the 6-month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient years with RoACTEMRA therapy. In the long-term exposure population the overall rate of gastrointestinal perforation was 0.28 events per 100 patient years. Reports of gastrointestinal perforation on RoACTEMRA were primarily reported as complications of diverticulitis including generalised purulent peritonitis, lower gastrointestinal perforation, fistulae and abscess.

Adverse events should be reported to Roche Products Limited. Please contact the Drug Safety Centre, Roche Products Limited, 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

Infusion reactions

In the 6-month 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 3778 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 3778 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 2876 patients have been tested for anti-tocilizumab antibodies in the 6-month controlled clinical trials. Of the 46 patients (1.6%) who developed anti-tocilizumab 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.

Haematological abnormalities

In the 6-month controlled trials decreases in neutrophil counts below 1 x 10^9/L occurred in 3.4% of patients on RoACTEMRA 8 mg/kg plus DMARDs compared to < 0.1% of patients on placebo plus DMARDs. Approximately half of the patients who developed an ANC < 1 x 10^9/L did so within 8 weeks after starting therapy. Decreases below 0.5 x 10^9/L were reported in 0.3% patients receiving RoACTEMRA 8 mg/kg plus DMARDs. Infections with neutropenia have been reported.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 6-month controlled clinical trials.

In the 6-month controlled trials decreases in platelet counts below 100 x 10^3/µL occurred in 1.7% of patients on RoACTEMRA 8 mg/kg plus DMARDs compared to < 1% on placebo plus DMARDs. These decreases occurred without associated bleeding events.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 6-month controlled clinical trials. Very rare reports of pancytopenia have occurred in the post marketing setting.

Adverse Drug Reactions (continued)

Hepatic transaminase elevations

During the 6-month controlled trials transient elevations in ALT/AST > 3 x ULN were observed in 2.1% of patients on RoACTEMRA 8 mg/kg compared to 4.9% of patients on MTX and in 6.5% of patients who received 8 mg/kg RoACTEMRA plus DMARDs compared to 1.5% of patients on placebo plus DMARDs.

The addition of potentially hepatotoxic drugs (e.g. MTX) to RoACTEMRA monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST > 5 x ULN were observed in 0.7% of RoACTEMRA monotherapy patients and 1.4% of RoACTEMRA plus DMARD patients, the majority of whom were discontinued permanently from RoACTEMRA treatment. These elevations were not associated with clinically relevant increase in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic impairment. During the double-blind controlled period, the incidence of indirect bilirubin greater than ULN upper limit of normal collected as a routine laboratory parameter is 6.2% in patients treated with 8 mg/kg RoACTEMRA plus DMARD. A total of 5.8% of patients experienced an elevation of indirect bilirubin of > 1-2 x ULN and 0.4% had an elevation > 2 x ULN.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevation in ALT/AST remained consistent with what was seen in the 6-month controlled clinical trials.

Lipid parameters

During the 6-month controlled trials, increases of lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol have been reported commonly. With routine laboratory monitoring it was seen that approximately 24% of patients receiving RoACTEMRA in clinical trials experienced sustained elevations in total cholesterol ≥ 6.2 mmol/L, with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/L. Elevations in lipid parameters responded to treatment with lipid-lowering agents.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevations in lipid parameters remained consistent with what was seen in the 6-month controlled trials.

Malignancies

The clinical data are insufficient to assess the potential incidence of malignancy following exposure to RoACTEMRA. 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.

Population pharmacokinetic analyses did not detect any effect of MTX, non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids on RoACTEMRA clearance.

There is no experience with the use of RoACTEMRA with TNF antagonists or other biological treatments for RA. RoACTEMRA is not recommended for use with other biological agents used for the treatment of RA. While transitioning from TNF antagonists to RoACTEMRA therapy, patients should be monitored for signs of infection and laboratory abnormalities, including neutrophil counts.

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 and 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, 3A4, 1A2 or 2C9 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin or benzodiazepines) should be monitored as doses may need to be increased. 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.

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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.

Women 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.

Breast feeding

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 breast-feeding or to continue/discontinue therapy with RoACTEMRA should be made taking into account the benefit of breast-feeding to the child and the benefit of RoACTEMRA therapy to the woman.

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 monitored closely in these patients.

Hepatic impairment

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

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Dosage and Administration

The recommended dose of RoACTEMRA for adult patients with RA is 8 mg/kg body weight given every 4 weeks as an intravenous infusion over 1 hour. 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 should be used concomitantly with MTX, but can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate
- RoACTEMRA has not been studied, and its use should be avoided, in combination with biological DMARDs such as TNF antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators because of the possibility of increased immunosuppression and increased risk of infection

General dose advice

- It is recommended that RoACTEMRA not be initiated in patients with an ANC < 2 x 10^9/L, platelet count < 50,000/µL, or who have ALT or AST > 5 x ULN
- Reduction of the dose from 8 mg/kg to 4 mg/kg is recommended for the management of elevated liver enzymes, neutropaenia or thrombocytopaenia

General considerations for administration

RoACTEMRA concentrate for intravenous (IV) infusion should be diluted to 100 mL by a healthcare professional using aseptic technique as follows:

- From a 100 mL infusion bag, withdraw a volume of 0.9% (9 mg/mL) sodium chloride injection equal to the volume of RoACTEMRA concentrate required for the patient's dose
- Slowly add the correct volume of RoACTEMRA concentrate for IV infusion from each vial into the infusion bag. To mix the concentrate, gently invert the bag to avoid foaming
- 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 microbiological point of view, the prepared solution for infusion should be used immediately. 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°C–8°C, unless dilution has taken place in controlled and validated aseptic conditions
- RoACTEMRA is supplied as a sterile concentrate that does 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
- After dilution, RoACTEMRA should be administered as an intravenous infusion over 1 hour
- 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

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Important Safety Information

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 patien ts 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 Limited,
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

Reference:
1. Summary of Product Characteristics for RoActemra® (tocilizumab). June 2012.

RoACTEMRA®
tocilizumab