RoACTEMRA for Systemic Juvenile Idiopathic Arthritis (sJIA)

HEALTHCARE PROFESSIONAL BROCHURE – IMPORTANT EFFICACY AND SAFETY INFORMATION

To assist healthcare professionals in assessing the benefits and risks associated with RoACTEMRA® (tocilizumab) therapy in patients with active sJIA

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

RoACTEMRA®
tocilizumab

Prescribing information can found on the back cover

Date of preparation: August 2011 RCUKACTE00258a

Contents

Indication and Usage

RoACTEMRA is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. RoACTEMRA can be given as monotherapy (in case of intolerance to methotrexate [MTX] or where treatment with MTX is inappropriate) or in combination with MTX.[1]

RoACTEMRA has been shown to be highly effective in reducing pain, fever and rash associated with sJIA and improving inflammatory arthritis and physical function.[1,2]

The efficacy and safety of RoACTEMRA for the treatment of active sJIA was assessed in a 12 week Phase III, randomised, double-blind, placebo-controlled, parallel-group, two-arm study.[1,2]

Patient Counselling Information and Laboratory Monitoring

Patient counselling information

Patients and parents/guardians of sJIA patients should be advised of the potential benefits and risks of RoACTEMRA.

- Infections:

Inform patients and parents/guardians of sJIA patients that RoACTEMRA may lower the patient's resistance to infection. Instruct them on the importance of contacting their doctor immediately when symptoms suggesting infection appear in order to ensure rapid evaluation and appropriate treatment.

RoACTEMRA®
tocilizumab

Patient Counselling Information and Laboratory Monitoring (continued)

- Hypersensitivity Reactions:

Inform patients and parents/guardians of sJIA patients about potentially serious hypersensitivity reactions. Serious hypersensitivity reactions including anaphylaxis have been reported in association with infusion of RoACTEMRA. Hypersensitivity 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.

In the 12 week controlled phase of the trial one event (angioedema) occurred during infusion which was considered serious and life threatening and lead to study treatment discontinuation. Events which may occur within 24 hours of infusion may include (but are not limited to):

- Rash
- Diarrhoea
- Arthralgia
- Urticaria
- Epigastric discomfort
- Headache

One of these events, urticaria, was considered serious

- Vaccinations:

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

- Before you administer RoACTEMRA, ask the patient or parents/guardians of sJIA patients if the patient:

  - Has an infection, is being treated for an infection or has a history of recurring infections
  - Has signs of an infection, such as a fever, cough or headache, or is feeling unwell
  - Has herpes zoster or any other skin infection with open sores
  - Has diabetes or other underlying conditions that may predispose him or her to infection
  - Has tuberculosis (TB), or has been in close contact with someone who has had TB
  - Is taking other biological drugs to treat sJIA, atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin or benzodiazepines
  - Has active hepatic disease or hepatic impairment
  - Has recently received a vaccination or is scheduled for any vaccination
  - Has cancer or a history of cancer
  - Is pregnant, wants to become pregnant, or breastfeeding
  - Is on a sodium restricted diet
  - Is known to be hypersensitive to RoACTEMRA or any of the excipients
  - Has haematological abnormalities, cardiovascular disorders or other risk factors

Laboratory monitoring

Alanine aminotransferase (ALT) and **aspartate aminotransferase** (AST) levels, **neutrophils** and **platelets** should be monitored at the time of the second infusion and thereafter according to good 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 in Section 4.4, Special warnings and precautions for use.

RoACTEMRA®
tocilizumab

Clinical Response[1]

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

The percentages of patients achieving JIA ACR30, 50, 70 and 90 responses are shown below.

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

Response Rate	RoACTEMRA (n = 75)	Placebo (n = 37)
JIA ACR30	90.7%*	24.3%
JIA ACR50	85.3%*	10.8%
JIA ACR70	70.7%*	8.1%
JIA ACR90	37.3%*	5.4%
p<0.0001, RoACTEMRA vs. placebo		

†TENDER: A global, multi-centre, Phase III, 3-Part, 5-Year trial which is ongoing, to determine the efficacy and safety of RoACTEMRA vs placebo in 112 patients with active sJIA. Patients were aged 2–17 years with active sJIA for ≥6 months and inadequate response to systemic corticosteroids and NSAIDs.[2]

Systemic effects

In the RoACTEMRA-treated patients, 85% who had fever due to sJIA at baseline were free of fever (no temperature recording ≥37.5°C in the preceding 14 days) at Week 12 versus 21% of placebo-treated patients (p<0.0001).

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

Corticosteroid tapering

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

Health-related and quality-of-life outcomes

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

Laboratory parameters

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

Warning 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) which may predispose patients to infections.

Vigilance for the timely detection of serious infection is recommended for patients receiving biological treatments for active sJIA, 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 and parents/guardians of sJIA patients should be instructed to contact their healthcare professional immediately when any symptoms suggesting infection appear, in order to ensure rapid evaluation and appropriate treatment.

Tuberculosis

As recommended for other biological treatments, sJIA 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.

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 / serious infusion related 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 reaction occurs, administration of RoACTEMRA should be stopped immediately and RoACTEMRA should be permanently discontinued.

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

RoACTEMRA®
tocilizumab

Warning and Precautions (continued)

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.

Vaccinations

Live and live-attenuated vaccines should not be given concurrently with RoACTEMRA as clinical safety has not been established. It is recommended that sJIA 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

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

Combination with TNF antagonists

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

Macrophage activation syndrome (MAS)

MAS is a serious life-threatening disorder that may develop in sJIA patients. In clinical trials, RoACTEMRA has not been studied in patients during an episode of active MAS. Please refer to the MAS card for further information.

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

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 at the time of second infusion and thereafter according to good 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 to >1 x 10^9/L resume RoACTEMRA
ANC <0.5	Discontinue RoACTEMRA The decision to discontinue RoACTEMRA for a laboratory abnormality should be based on the medical assessment of the individual patient

- Platelets

Decreases in platelet counts have occurred following treatment with RoACTEMRA. Caution should be exercised when considering initiation of RoACTEMRA treatment in patients with a low platelet count (i.e. platelet count below 100 x 10^3/µL). In patients with a platelet count <50 x 10^3/µL, treatment is not recommended.

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

Low platelet count

Laboratory Value (cells x 10^3/µL)	Action
50 to 100	Modify dose of concomitant MTX if appropriate Interrupt RoACTEMRA dosing When platelet count is > 100 x 10^3/µl resume RoACTEMRA
<50	Discontinue RoACTEMRA The decision to discontinue RoACTEMRA for a laboratory abnormality should be based on the medical assessment of the individual patient

RoACTEMRA® tocilizumab

Warning and Precautions (continued)

- 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.

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.

In sJIA patients, ALT and AST levels should be monitored at the time of the second infusion and thereafter according to good clinical practice.

Liver enzyme abnormalities

Laboratory Value	Action
>1 to 3 x ULN	Modify dose of concomitant MTX if appropriate For persistent increases in this range, interrupt RoACTEMRA until ALT/AST have normalised
>3 to 5 x ULN	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 The decision to discontinue RoACTEMRA for a laboratory abnormality should be based on the medical assessment of the individual patient

- Lipids

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

Adverse drug reactions

The safety of tocilizumab in sJIA has been studied in 112 patients from 2 to 17 years of age. In the 12 week double-blind, controlled phase, 75 patients received treatment with tocilizumab (8 mg/kg or 12 mg/kg based upon body weight). After 12 weeks or at the time of switching to tocilizumab, due to disease worsening, patients were treated in the ongoing open label extension phase.

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

Infections

In the 12-week controlled phase of the clinical study, the rate of all infections in the RoACTEMRA group was 344.7 per 100 patient-years compared with 287.0 per 100 patient-years in the placebo group. In the ongoing open-label extension phase of the study, the overall rate of infections remained similar at 306.6 per 100 patient-years.

In the 12-week controlled phase of the clinical study, the rate of serious infections in the RoACTEMRA group was 11.5 per 100 patient-years. At 1 year in the ongoing open-label extension phase of the study, the overall rate of serious infections remained stable at 11.3 per 100 patient-years.

Reported serious infections were similar to those seen in RA patients with the addition of varicella and otitis media.

Infusion Reactions

Infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion. In the 12-week controlled phase of the clinical study, 4% of patients from the RoACTEMRA group experienced events occurring during infusion. One event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment.

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

Clinically significant hypersensitivity reactions associated with RoACTEMRA and requiring treatment discontinuation were reported in <1% (1/112) of patients treated with RoACTEMRA during the controlled period and up to and including the open-label clinical study.

Immunogenicity

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

RoACTEMRA®
tocilizumab

Adverse drug reactions (continued)

Neutrophils

During routine laboratory monitoring in the 12-week controlled phase of the clinical study, a decrease in neutrophil counts below 1 x 10^9/l occurred in 7% of patients in the RoACTEMRA group, and no decreases in the placebo group.

In the ongoing open-label extension phase, decreases in neutrophil counts below 1 x 10^9/l occurred in 15% of the RoACTEMRA group. There was no clear relationship between decreases in neutrophils below 1 x 10^9/l and the occurrence of serious infections.

Platelets

During routine laboratory monitoring in the 12-week controlled phase, 3% of patients in the placebo group and 1% in the RoACTEMRA group had a decrease in platelet count to ≤100 x 10^3/µl.

In the ongoing open-label extension phase, decreases in platelet counts below 100 x 10^3/µl occurred in 3% of patients in the RoACTEMRA group, without associated bleeding events.

Hepatic transaminase elevations

During routine laboratory monitoring in the 12-week controlled phase, elevation in ALT or AST ≥3 x ULN occurred in 5% and 3% of patients, respectively, in the RoACTEMRA group, and 0% in the placebo group.

In the ongoing open-label extension phase, elevation in ALT or AST ≥3 x ULN occurred in 12% and 4% of patients, respectively, in the RoACTEMRA group.

Immunoglobulin G

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

Lipid parameters

During routine laboratory monitoring in the 12-week controlled phase, elevation in total cholesterol >1.5 x ULN to 2 x ULN occurred in 1.5% of the RoACTEMRA group and none in the placebo group. Elevation in LDL >1.5 x ULN to 2 x ULN occurred in 1.9% of patients in the RoACTEMRA group, and none in the placebo group.

In the ongoing open label extension phase, the pattern and incidence of elevations in lipid parameters remained consistent with the 12 week controlled phase data.

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 of the use of RoACTEMRA with TNF antagonists or other biological treatments for sJIA patients. RoACTEMRA is not recommended for use with other biological agents.

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, 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 adjusted 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 Special Populations

Paediatric patients

The safety and efficacy of RoACTEMRA in patients below 2 years of age has not been established. No data are available.

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.

RoACTEMRA®
tocilizumab

Use in Special Populations (continued)

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.

Lactation

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 woman.

Dosage and Administration

The recommended dose of RoACTEMRA in sJIA patients is 8 mg/kg once every 2 weeks in patients weighing ≥30 kg, or 12 mg/kg once every 2 weeks in patients weighing <30 kg. The dose should be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time.

- RoACTEMRA can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX

General dose advice

- Dose interruptions of RoACTEMRA for laboratory abnormalities are recommended (see tables on pages 7 and 8)
- Reduction of RoACTEMRA dose due to laboratory abnormalities has not been studied in sJIA
- If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and RoACTEMRA dosing interrupted until the clinical situation has been evaluated

- The decision to discontinue RoACTEMRA for a laboratory abnormality should be based upon the medical assessment of the individual patient
- Available clinical data suggest that clinical improvement is observed within 6 weeks of initiation of treatment with RoACTEMRA. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe

General considerations for administration

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

For Patients <30 kg

- From a 50 ml infusion bag, withdraw a volume of sterile, non-pyrogenic 0.9% (9 mg/ml) sodium chloride solution for injection equal to the volume of RoACTEMRA concentrate required for the patient's dose under aseptic conditions

For Patients ≥30 kg

- From a 100 ml infusion bag, withdraw a volume of sterile, non-pyrogenic 0.9% (9 mg/ml) sodium chloride 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
- 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
- Allow the fully diluted RoACTEMRA solution to reach room temperature prior to infusion
- The infusion should be administered over 1 hour 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 drugs
- Adverse events should be reported. Reporting forms and information can be found at www.medicinesauthority.gov.mt/pub/adr.doc. Adverse events should also be reported to Roche Products Limited. Please contact UK Drug Safety Centre on: +44 1707 367554

RoACTEMRA®
tocilizumab

PRESCRIBING INFORMATION ROACTEMRA® (tocilizumab):Please refer to RoActemra SPC for full prescribing information. Indication: RoActemra, in combination with methotrexate (MTX), is indicated for the treatment of adult patients with moderate to severe active rheumatoid arthritis who have had an inadequate response or intolerance to previous DMARDs or TNF antagonists. 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. Also, in combination with MTX, for the treatment of active systemic juvenile idiopathic arthritis (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). **Dosage and Administration: RA:** Recommended posology is 8mg/kg iv infusion given every 4 weeks. For patients with body weight over 100kg, doses exceeding 800mg per infusion are not recommended. Doses above 1.2g have not been evaluated. **sJIA:** Recommended posology is 8mg/kg for patients weighing ≥30kg or 12mg/kg for patients weighing <30kg, given every 2 weeks. Infusions should be given over 1 hour, with 8mg/kg diluted to a volume of 100ml and 12mg/kg diluted to a volume of 50ml. Treatment should be initiated by an appropriately experienced healthcare professional and patients should be given the Patient Alert Card. **Dose adjustments: RA:** No dose adjustments are required in elderly patients, or in patients with mild renal impairment. Dose reduction to 4mg/kg, or interruptions, are recommended in the event of raised liver enzymes, low absolute neutrophil count or low platelet count (see SPC for details). RoActemra should not be initiated in patients with absolute neutrophil count below $2x10^9$/l. **sJIA:** Dose interruptions are recommended in the event of raised liver enzymes, low absolute neutrophil count or low platelet count but dose reductions have not been studied in these patients (see SPC for details). **Contraindications:** Hypersensitivity to any component of the product; active, severe infections. **Precautions: both indications:** *Infections:* Serious and sometimes fatal infections have been reported with RoActemra. In cases of serious infection interrupt therapy until controlled. Caution in patients with recurring/chronic infections, or other conditions which may predispose to infection. Severe neutropenia may be associated with an increased risk of serious infections. *Tuberculosis:* Screen for and treat latent TB prior to starting therapy. *Hypersensitivity reactions:* Fatal anaphylaxis may occur 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. If serious hypersensitivity/serious infusion related reactions occur stop RoActemra treatment and permanently discontinue. *Active hepatic disease/impairment:* Use with caution in patients with active hepatic disease/impairment. *Hepatic transaminase elevations:* Not recommended in patients with baseline ALT or AST >5xULN; caution in patients with ALT or AST >1.5xULN. Monitor ALT/AST levels according to SPC. Consider other liver function tests including bilirubin if clinically indicated. *Haematological abnormalities:* Caution in patients with platelet count $<100x10^3$/µl; monitor levels according to SPC. If reduced, follow recommendations for dose modification. Continued treatment not recommended in patients with ANC <0.5 x 10^9/ l or platelet count <50 x 10^3/µl. *Lipid parameters:* Lipid parameters should be assessed according to SPC, if elevated, patients should be managed according to local guidelines for hyperlipidaemia. *Neurological disorders:* The potential for central demyelination with RoActemra is currently unknown; physicians should be vigilant for symptoms of new onset disease. *Malignancy:* Immunomodulatory medicines may increase the risk of malignancy. *Vaccinations:* Live and live attenuated vaccines should not be given concurrently as safety has not been established. *Cardiovascular risk:* RA patients should have CV risk factors managed as part of usual standard of care. *Combined with other biologic treatments:* Not recommended due to lack of experience. *Sodium:* Product contains 26.55mg sodium per 1200mg. **RA only:** *Viral reactivation:* Viral reactivation (e.g. hepatitis B virus) has been reported with biologic therapies for RA. *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 medicines which are individually adjusted and metabolised via CYP450 3A4, 1A2, or 2C9 should be monitored when starting or stopping RoActemra, as doses may need adjusting. **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:** Most commonly reported ADRs were URTI, nasopharyngitis, headache, hypertension and increased ALT. *Very common ADR:* hypercholesterolaemia. *Common ADRs:* cellulitis, pneumonia, oral herpes simplex, herpes zoster, abdominal pain, mouth ulceration, gastritis, rash, pruritis, urticaria, dizziness, weight increased, total bilirubin increased, leukopenia, neutropenia, peripheral oedema, hypersensitivity reactions, conjunctivitis, cough, dyspnoea. *Medically significant events: Infections:* Serious infections have been reported, some with fatal outcome. Opportunistic infections have been reported. *GI perforations:* primarily reported as complications of diverticulitis. *Infusion reactions:* Hypersensitivity reactions requiring treatment discontinuation occurred in 0.3% of patients treated with tocilizumab. Reactions were generally observed during the 2^{nd}-5^{th} 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:* Hypersensitivity reactions requiring treatment discontinuation occurred in <1% of patients treated with tocilizumab. *IgG:* IgG levels decreased during therapy. *Other:* decreased neutrophil count, decreased platelet count, hepatic transaminase elevations, lipid parameter increases. For all indications, prescriber should consult the SPC in relation to other side-effects. **Legal category:** POM **Presentations and Basic NHS Costs:** 80mg of tocilizumab in 4ml (20mg/ml) 1 vial: £102.40, 200mg of tocilizumab in 10ml (20mg/ml) 1 vial: £256.00, 400mg of tocilizumab in 20ml (20mg/ml) 1 vial: £512.00 **Marketing Authorisation Numbers:** EU/1/08/492/01 (80mg), EU/1/08/492/03 (200mg), EU/1/08/492/05 (400mg) **Marketing Authorisation Holder:** Roche Registration Limited, 6 Falcon Way, Welwyn Garden City, Herts AL7 1TW. RoActemra is a registered trade mark. **Date of Prep:** August 2011 RCUKMEDI00006a

Adverse events should be reported to Roche Products Limited. Please contact UK Drug Safety Centre, Roche Products Ltd, 6 Falcon Way, Shire Park, Welwyn Garden City, Hertfordshire, England Telephone number +44 1707 367554. Adverse events may otherwise be reported via the yellow card scheme. Reporting forms and information can be found at: http://www.medicinesauthority.gov.mt/pub/adr.doc.

References

1. RoACTEMRA (tocilizumab) Summary of Product Characteristics, August 2011; http://medicines.org.uk/EMC
2. De Benedetti F, Brunner H, Ruperto N, *et al*. [1434] - *Tocilizumab in Patients with Systemic Juvenile Idiopathic Arthritis: Efficacy Data from the Placebo-Controlled 12-Week* Part of the Phase 3 TENDER Trial. Arthritis Rheum 2010; 62 (10 suppl): S596