

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 20 mg/ml concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml concentrate contains 20 mg tocilizumab*.

Each vial contains 80 mg of tocilizumab* in 4 ml (20 mg/ml).

Each vial contains 200 mg of tocilizumab* in 10 ml (20 mg/ml).

Each vial contains 400 mg of tocilizumab* in 20 ml (20 mg/ml).

*humanised IgG1 monoclonal antibody against the human interleukin-6 (IL-6) receptor produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipients with known effects

Each 80 mg vial contains 0.10 mmol (2.21 mg) sodium.

Each 200 mg vial contains 0.20 mmol (4.43 mg) sodium.

Each 400 mg vial contains 0.39 mmol (8.85 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to opalescent, colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RoActemra, in combination with methotrexate (MTX), is indicated for:

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
- the treatment of moderate to severe active 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 methotrexate.

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 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.

RoActemra in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX.

RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

4.2 Posology and method of administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA, sJIA or pJIA.

All patients treated with RoActemra should be given the Patient Alert Card.

RA Patients

Posology

The recommended posology is 8 mg/kg body weight, given once every four weeks.

For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended (see section 5.2).

Doses above 1.2 g have not been evaluated in clinical studies (see section 5.1).

Dose adjustments due to laboratory abnormalities (see section 4.4).

- Liver enzyme abnormalities

Laboratory Value	Action
> 1 to 3 x Upper Limit of Normal (ULN)	<p>Modify the dose of the concomitant MTX if appropriate</p> <p>For persistent increases in this range, reduce RoActemra dose to 4 mg/kg or interrupt RoActemra until alanine aminotransferase (ALT) or aspartate aminotransferase (AST) have normalised</p> <p>Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate</p>
> 3 to 5 x ULN (confirmed by repeat testing, see section 4.4).	<p>Interrupt RoActemra dosing until < 3 x ULN and follow recommendations above for > 1 to 3 x ULN</p> <p>For persistent increases > 3 x ULN, discontinue RoActemra</p>
> 5 x ULN	Discontinue RoActemra

- Low absolute neutrophil count (ANC)

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

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

- Low platelet count

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

Special populations

Paediatric patients

sJIA Patients

The recommended posology in patients above 2 years of age is 8 mg/kg once every 2 weeks in patients weighing greater than or equal to 30 kg or 12 mg/kg once every 2 weeks in patients weighing less than 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.

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

Dose interruptions of tocilizumab for the following laboratory abnormalities are recommended in sJIA patients in the tables below. If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many co-morbid conditions that may affect laboratory values in sJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.

- Liver enzyme abnormalities

Laboratory Value	Action
> 1 to 3 x ULN	Modify the dose of the concomitant MTX if appropriate For persistent increases in this range, interrupt RoActemra until ALT/AST have normalized.
> 3 x ULN to 5x ULN	Modify the dose of the concomitant MTX if appropriate Interrupt RoActemra dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN
> 5x ULN	Discontinue RoActemra. The decision to discontinue RoActemra in sJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low absolute neutrophil count (ANC)

Laboratory Value (cells x 10⁹/l)	Action
ANC > 1	Maintain 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 in sJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low platelet count

Laboratory Value (cells x 10³/μl)	Action
50 to 100	Modify the dose of the 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 in sJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

Reduction of tocilizumab dose due to laboratory abnormalities has not been studied in sJIA patients.

Available 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.

pJIA Patients

The recommended posology in patients above 2 years of age is 8 mg/kg once every 4 weeks in patients weighing greater than or equal to 30 kg or 10 mg/kg once every 4 weeks in patients weighing less than 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.

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

Dose interruptions of tocilizumab for the following laboratory abnormalities are recommended in pJIA patients in the tables below. If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many co-morbid conditions that may effect laboratory values in pJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.

- Liver enzyme abnormalities

Laboratory Value	Action
> 1 to 3 x ULN	Modify the dose of the concomitant MTX if appropriate For persistent increases in this range, interrupt RoActemra until ALT/AST have normalized.
> 3 x ULN to 5x ULN	Modify the dose of the concomitant MTX if appropriate Interrupt RoActemra dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN
> 5x ULN	Discontinue RoActemra. The decision to discontinue RoActemra in pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low absolute neutrophil count (ANC)

Laboratory Value (cells x 10⁹/l)	Action
ANC > 1	Maintain 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 in pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low platelet count

Laboratory Value (cells x 10³/μl)	Action
50 to 100	Modify the dose of the 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 in pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

Reduction of tocilizumab dose due to laboratory abnormalities has not been studied in pJIA patients.

Available data suggest that clinical improvement is observed within 12 weeks of initiation of treatment with RoActemra. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe.

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 (see section 5.2). 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.

Method of administration

After dilution, RoActemra for RA, sJIA and pJIA patients should be administered as an intravenous infusion over 1 hour.

RA, sJIA and pJIA Patients ≥ 30 kg

RoActemra should be diluted to a final volume of 100 ml with sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection using aseptic technique.

For instructions on dilution of the medicinal product before administration, see section 6.6.

sJIA and pJIA Patients < 30 kg

RoActemra should be diluted to a final volume of 50 ml with sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection using aseptic technique.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including RoActemra (see section 4.8, undesirable effects). RoActemra treatment must not be initiated in patients with active infections (see section 4.3). Administration of RoActemra should be interrupted if a patient develops a serious infection until the infection is controlled (see section 4.8). Healthcare professionals should exercise caution when considering the use of RoActemra in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes and interstitial lung disease which may predispose patients to infections).

Vigilance for the timely detection of serious infection is recommended for patients receiving biological treatments for moderate to severe RA, sJIA or pJIA as signs and symptoms of acute inflammation may be lessened, associated with suppression of the acute phase reaction. The effects of tocilizumab on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients (which includes younger children with sJIA or pJIA who may be less able to communicate their symptoms) and parents/guardians of sJIA or pJIA 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, RA, sJIA and pJIA patients should be screened for latent tuberculosis (TB) infection prior to starting RoActemra therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating RoActemra. Prescribers are reminded of the risk of false negative tuberculin skin and interferon-gamma TB blood test results, especially in patients who are severely ill or immunocompromised.

Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur during or after therapy with RoActemra.

Viral reactivation

Viral reactivation (e.g. hepatitis B virus) has been reported with biologic therapies for RA. In clinical studies with tocilizumab, 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 in RA patients (see section 4.8). RoActemra should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis which can be associated with gastrointestinal perforation.

Hypersensitivity reactions

Serious hypersensitivity reactions have been reported in association with infusion of RoActemra (see section 4.8). 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.

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 (see sections 4.2 and 4.8).

Hepatic transaminase elevations

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 (see section 4.8). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with RoActemra. When clinically indicated, other liver function tests including bilirubin should be considered.

Caution should be exercised when considering initiation of RoActemra treatment in patients with elevated ALT or AST $> 1.5 \times \text{ULN}$. In patients with baseline ALT or AST $> 5 \times \text{ULN}$, treatment is not recommended.

In RA patients, 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 recommended modifications based on transaminases see section 4.2. For ALT or AST elevations $> 3\text{--}5 \times \text{ULN}$, confirmed by repeat testing, RoActemra treatment should be interrupted.

In sJIA and pJIA patients, ALT and AST levels should be monitored at the time of the second infusion and thereafter according to good clinical practice, see section 4.2.

Haematological abnormalities

Decreases in neutrophil and platelet counts have occurred following treatment with tocilizumab 8 mg/kg in combination with MTX (see section 4.8). There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist.

In patients not previously treated with RoActemra, initiation is not recommended in patients with an absolute neutrophil count (ANC) below $2 \times 10^9/\text{l}$. Caution should be exercised when considering initiation of RoActemra treatment in patients with a low platelet count (i.e. platelet count below $100 \times 10^3/\mu\text{l}$). In patients who develop an ANC $< 0.5 \times 10^9/\text{l}$ or a platelet count $< 50 \times 10^3/\mu\text{l}$, continued treatment is not recommended.

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 RA patients, neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. For recommended dose modifications based on ANC and platelet counts, see section 4.2.

In sJIA and pJIA patients, neutrophils and platelets should be monitored at the time of second infusion and thereafter according to good clinical practice, see section 4.2.

Lipid parameters

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

section 4.8). In the majority of patients, there was no increase in atherogenic indices, and elevations in total cholesterol responded to treatment with lipid lowering agents.

In sJIA, pJIA and RA patients, assessment of lipid parameters should be performed 4 to 8 weeks following initiation of RoActemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

Neurological disorders

Physicians should be vigilant for symptoms potentially indicative of new-onset central demyelinating disorders. The potential for central demyelination with RoActemra is currently unknown.

Malignancy

The risk of malignancy is increased in patients with RA. Immunomodulatory medicinal products may increase the risk of malignancy.

Vaccinations

Live and live attenuated vaccines should not be given concurrently with RoActemra as clinical safety has not been established. In a randomized open-label study, adult RA patients treated with RoActemra and MTX were able to mount an effective response to both the 23-valent pneumococcal polysaccharide and tetanus toxoid vaccines which was comparable to the response seen in patients on MTX only. It is recommended that all patients, particularly sJIA and pJIA patients, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating RoActemra therapy. The interval between live vaccinations and initiation of RoActemra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

Cardiovascular risk

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

Combination with TNF antagonists

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

Sodium

This medicinal product contains 1.17 mmol (or 26.55 mg) sodium per maximum dose of 1200 mg. To 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'.

Paediatric population

sJIA Patients

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

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Concomitant administration of a single dose of 10 mg/kg tocilizumab with 10-25 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 tocilizumab clearance.

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 tocilizumab, is introduced.

In vitro studies with cultured human hepatocytes demonstrated that IL-6 caused a reduction in CYP1A2, CYP2C9, CYP2C19 and CYP3A4 enzyme expression. Tocilizumab 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 tocilizumab, to the level similar to, or slightly higher than, those observed in healthy subjects.

When starting or stopping therapy with tocilizumab, patients taking medicinal products which are individually adjusted and are metabolised via CYP450 3A4, 1A2 or 2C9 (e.g. . methylprednisolone, dexamethasone, (with the possibility for oral glucocorticoid withdrawal syndrome), atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses may need to be increased to maintain therapeutic effect. Given its long elimination half-life ($t_{1/2}$), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

Pregnancy

There are no adequate data from the use of tocilizumab in pregnant women. A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose (see section 5.3). The potential risk for humans is unknown.

RoActemra should not be used during pregnancy unless clearly necessary.

Breast-feeding

It is unknown whether tocilizumab is excreted in human breast milk. The excretion of tocilizumab 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.

Fertility

Available non-clinical data do not suggest an effect on fertility under tocilizumab treatment.

4.7 Effects on ability to drive and use machines

RoActemra has minor influence on the ability to drive and use machines (see section 4.8, dizziness).

4.8 Undesirable effects

RA Patients

Summary of the safety profile

The most commonly reported ADRs (occurring in $\geq 5\%$ of patients treated with tocilizumab monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

The most serious ADRs were serious infections, complications of diverticulitis, and hypersensitivity reactions.

RA Patients

The safety of tocilizumab has been studied in 4 placebo-controlled studies (studies II, III, IV and V), 1 MTX-controlled study (study I) and their extension periods (see section 5.1).

The double-blind controlled period was 6 months in four studies (studies I, III, IV and V) and was up to 2 years in one study (study II). In the double-blind controlled studies, 774 patients received tocilizumab 4 mg/kg in combination with MTX, 1870 patients received tocilizumab 8 mg/kg in combination with MTX or other DMARDs and 288 patients received tocilizumab 8 mg/kg monotherapy.

The long-term exposure population includes all patients who received at least one dose of tocilizumab either in the double-blind control period or open label extension phase in the studies. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3296 for at least one year, 2806 received treatment for at least 2 years and 1222 for 3 years.

The ADRs listed in Table 1 are presented by system organ class and frequency categories, defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($> 1/10,000$ to $< 1/1,000$) or very rare ($< 1/10,000$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. Summary of ADRs occurring in patients with RA receiving tocilizumab as monotherapy or in combination with MTX or other DMARDs in the double-blind controlled period

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

* Includes elevations collected as part of routine laboratory monitoring (see text below)

Infections

In the 6-month controlled studies the rate of all infections reported with tocilizumab 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 tocilizumab 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 tocilizumab group and 1.5 events per 100 patient years of exposure in the MTX group.

In the long-term exposure population, the overall rate of serious infections (bacterial, viral and fungal) was 4.7 events per 100 patient years. Reported serious infections, some with fatal outcome, included active tuberculosis, which may present with intrapulmonary or extrapulmonary disease, invasive pulmonary infections, including candidiasis, aspergillosis, coccidioidomycosis and pneumocystis

jirovecii, pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported.

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.

Gastrointestinal Perforation

During the 6-month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient years with tocilizumab 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 tocilizumab were primarily reported as complications of diverticulitis including generalised purulent peritonitis, lower gastrointestinal perforation, fistulae and abscess.

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 tocilizumab 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 8/4,009 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 tocilizumab and requiring treatment discontinuation were reported in a total of 56 out of 4,009 patients (1.4%) treated with tocilizumab during the controlled and open label clinical studies. These reactions were generally observed during the second to fifth infusions of tocilizumab (see section 4.4). Fatal anaphylaxis has been reported after marketing authorisation during treatment with tocilizumab (see section 4.4).

Immunogenicity

A total of 2,876 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:

Neutrophils

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

Platelets

In the 6-month controlled trials decreases in platelet counts below $100 \times 10^3/\mu l$ occurred in 1.7% of patients on tocilizumab 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.

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 tocilizumab 8 mg/kg compared to 4.9% of patients on MTX and in 6.5% of patients who received 8 mg/kg tocilizumab plus DMARDs compared to 1.5% of patients on placebo plus DMARDs.

The addition of potentially hepatotoxic drugs (e.g. MTX) to tocilizumab monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST > 5 x ULN were observed in 0.7% of tocilizumab monotherapy patients and 1.4% of tocilizumab plus DMARD patients, the majority of whom were discontinued permanently from tocilizumab 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 the upper limit of normal, collected as a routine laboratory parameter, is 6.2% in patients treated with 8 mg/kg tocilizumab + DMARD. A total of 5.8% of patients experienced an elevation of indirect bilirubin of > 1 to 2 x ULN and 0.4% had an elevation of > 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 tocilizumab. Long-term safety evaluations are ongoing.

Skin Reactions

Very rare reports of Stevens-Johnson Syndrome have occurred in the post marketing setting.

Paediatric population

The safety of tocilizumab in the pediatric population in the sections on pJIA and sJIA below. In general, the ADRs in pJIA and sJIA patients were similar in type to those seen in RA patients, see section 4.8.

The ADRs in the pJIA and sJIA patients treated with tocilizumab are described below and are presented in the Table 2 by system organ class and frequency categories, defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$) or uncommon ($\geq 1/1,000$ to $< 1/100$)

Table 2: Summary of ADRs occurring in patients with sJIA or pJIA receiving tocilizumab as monotherapy or in combination with MTX.

SOC	PT	Frequency		
Infections and Infestations		Very Common	Common	Uncommon
	Upper Respiratory Tract Infections	pJIA, sJIA		
	Nasopharyngitis	pJIA, sJIA		
Gastrointestinal Disorders				
	Nausea		pJIA	
	Diarrhea		pJIA, sJIA	
General disorders and administration site conditions				
	Infusion related reactions		pJIA ¹ , sJIA ²	
Nervous system disorders				
	Headache	pJIA	sJIA	
Investigations				
	Hepatic transaminases increased		pJIA	
	Decrease in neutrophil count	sJIA	pJIA	
	Platelet count decreased		sJIA	pJIA
	Cholesterol increased		sJIA	pJIA

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

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

pJIA Patients

The safety of tocilizumab in pJIA has been studied in 188 patients from 2 to 17 years of age. The total patient exposure was 184.4 patient years. The frequency of ADRs in pJIA patients can be found in Table 2. The types of ADRs in pJIA patients were similar to those seen in RA and sJIA patients, see section 4.8. When compared to the adult RA population, events of nasopharyngitis, headache, nausea, and decreased neutrophil count were more frequently reported in the pJIA population. Events of cholesterol increased were less frequently reported in the pJIA population than in the adult RA population.

Infections

The rate of infections in the tocilizumab all exposure population was 163.7 per 100 patient years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was numerically higher in patients weighing <30 kg treated with 10 mg/kg tocilizumab (12.2 per 100 patient years) compared to patients weighing ≥30 kg, treated with 8 mg/kg tocilizumab (4.0 per 100 patient years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing <30 kg treated with 10 mg/kg tocilizumab (21.4%) compared to patients weighing ≥30 kg, treated with 8 mg/kg tocilizumab (7.6%).

Infusion Reactions

In pJIA patients, infusion related reactions are defined as all events occurring during or within 24 hours of an infusion. In the tocilizumab all exposure population, 11 patients (5.9%) experienced infusion reactions during the infusion and 38 patients (20.2%) experienced an event within 24 hours of an infusion. The most common events occurring during infusion were headache, nausea and hypotension and within 24 hours of infusion were dizziness and hypotension. In general, the adverse drug reactions observed during or within 24 hours of an infusion were similar in nature to those seen in RA and sJIA patients, see section 4.8.

No clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported.

Immunogenicity

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

Neutrophils

During routine laboratory monitoring in the tocilizumab all exposure population, a decrease in neutrophil count below $1 \times 10^9/L$ occurred in 3.7% of patients.

Platelets

During routine laboratory monitoring in the tocilizumab all exposure population, 1% of patients had a decrease in platelet count to $\leq 50 \times 10^3/\mu L$ without associated bleeding events.

Hepatic transaminase elevations

During routine laboratory monitoring in the tocilizumab all exposure population, elevation in ALT or AST $\geq 3 \times \text{ULN}$ occurred in 3.7% and <1% of patients, respectively.

Lipid parameters

During routine laboratory monitoring in the tocilizumab all exposure population, elevation in total cholesterol $>1.5\text{-}2 \times \text{ULN}$ occurred in one patient (0.5%) and elevation in LDL $>1.5\text{-}2 \times \text{ULN}$ in one patient (0.5%).

sJIA Patients

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 ADRs in sJIA patients were similar in type to those seen in RA patients, see section 4.8. The frequency of ADRs in sJIA patients can be found in Table 2. When compared to the adult RA population, patients with sJIA experienced a higher frequency of nasopharyngitis, decrease in neutrophil counts, hepatic transaminases increased, and diarrhea. Events of cholesterol increased were less frequently reported in the sJIA population than in the adult RA population.

Infections

In the 12 week controlled phase, the rate of all infections in the tocilizumab group was 344.7 per 100 patient years and 287.0 per 100 patient years in the placebo group. In the ongoing open label extension phase (Part II), the overall rate of infections remained similar at 306.6 per 100 patient years.

In the 12 week controlled phase, the rate of serious infections in the tocilizumab group was 11.5 per 100 patient years. At one year in the ongoing open label extension phase 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, 4% of patients from the tocilizumab 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, diarrhea, epigastric discomfort, arthralgia and headache. One of these events, urticaria, was considered serious.

Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation, were reported in 1 out of 112 patients (< 1%) treated with tocilizumab during the controlled and up to and including the open label clinical trial.

Immunogenicity

All 112 patients 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.

Neutrophils

During routine laboratory monitoring in the 12 week controlled phase, a decrease in neutrophil counts below $1 \times 10^9/l$ occurred in 7% of patients in the tocilizumab group, and no decreases in the placebo group.

In the ongoing open label extension phase, decreases in neutrophil counts below $1 \times 10^9/l$, occurred in 15% of the tocilizumab group.

Platelets

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

In the ongoing open label extension phase, decreases in platelet counts below $100 \times 10^3/\mu l$, occurred in 3% of patients in the tocilizumab group, without associated bleeding events.

Hepatic transaminase elevations

During routine laboratory monitoring in the 12 week controlled phase, elevation in ALT or AST $\geq 3 \times$ ULN occurred in 5% and 3% of patients, respectively, in the tocilizumab group, and 0% in the placebo group.

In the ongoing open label extension phase, elevation in ALT or AST $\geq 3 \times$ ULN occurred in 12% and 4% of patients, respectively, in the tocilizumab group.

Immunoglobulin G

IgG levels decrease during therapy. A decrease to the lower limit of normal 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 $> 1.5 \times$ ULN to $2 \times$ ULN occurred in 1.5% of the tocilizumab group and none in the placebo group. Elevation in LDL $> 1.5 \times$ ULN to $2 \times$ ULN occurred in 1.9% of patients in the tocilizumab group, and in 0% of 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

There are limited data available on overdose with RoActemra. One case of accidental overdose was reported in which a patient with multiple myeloma received a single dose of 40 mg/kg. No adverse reactions were observed.

No serious adverse reactions were observed in healthy volunteers who received a single dose up to 28 mg/kg, although dose limiting neutropenia was observed.

Paediatric population

No case of an overdose in the paediatric population has been observed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors; ATC code: L04AC07.

Mechanism of action

Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis and neoplasia.

RA Patients

Pharmacodynamic effects

In clinical studies with tocilizumab, rapid decreases in CRP, erythrocyte sedimentation rate (ESR) and serum amyloid A (SAA) were observed. Consistent with the effect on acute phase reactants, treatment with tocilizumab was associated with reduction in platelet count within the normal range. Increases in haemoglobin levels were observed, through tocilizumab decreasing the IL-6 driven effects on hepcidin production to increase iron availability. In tocilizumab-treated patients, decreases in the levels of CRP to within normal ranges were seen as early as week 2, with decreases maintained while on treatment.

In healthy subjects administered tocilizumab in doses from 2 to 28 mg/kg, absolute neutrophil counts decreased to their lowest 3 to 5 days following administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. Rheumatoid arthritis patients demonstrated a similar pattern of absolute neutrophil counts following tocilizumab administration (see section 4.8).

Clinical efficacy and safety

The efficacy of tocilizumab 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 eight tender and six swollen joints at baseline.

In Study I, tocilizumab was administered intravenously every four weeks as monotherapy. In Studies II, III and V, tocilizumab was administered intravenously every four weeks in combination with MTX vs. placebo and MTX. In Study IV, tocilizumab was administered intravenously every 4 weeks in combination with other DMARDs vs. placebo and other DMARDs. The primary endpoint for each of the five studies was the proportion of patients who achieved an ACR 20 response at week 24.

Study I evaluated 673 patients who had not been treated with MTX within six months prior to randomisation and who had not discontinued previous MTX treatment as a result of clinically

important toxic effects or lack of response. The majority (67%) of patients were MTX-naïve. Doses of 8 mg/kg of tocilizumab were given every four weeks as monotherapy. The comparator group was weekly MTX (dose titrated from 7.5 mg to a maximum of 20 mg weekly over an eight week period).

Study II, a two year study with planned analyses at week 24, week 52 and week 104, evaluated 1,196 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of tocilizumab or placebo were given every four weeks as blinded therapy for 52 weeks in combination with stable MTX (10 mg to 25 mg weekly). After week 52, all patients could receive open-label treatment with tocilizumab 8 mg/kg. Of the patients who completed the study who were originally randomised to placebo + MTX, 86% received open-label tocilizumab 8 mg/kg in year 2. The primary endpoint at week 24 was the proportion of patients who achieved an ACR 20 response. At week 52 and week 104 the co-primary endpoints were prevention of joint damage and improvement in physical function.

Study III evaluated 623 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg tocilizumab or placebo were given every four weeks, in combination with stable MTX (10 mg to 25 mg weekly).

Study IV evaluated 1,220 patients who had an inadequate response to their existing rheumatologic therapy, including one or more DMARDs. Doses of 8 mg/kg tocilizumab or placebo were given every four weeks in combination with stable DMARDs.

Study V evaluated 499 patients who had an inadequate clinical response or were intolerant to one or more TNF antagonist therapies. The TNF antagonist therapy was discontinued prior to randomisation. Doses of 4 or 8 mg/kg tocilizumab or placebo were given every four weeks in combination with stable MTX (10 mg to 25 mg weekly).

Clinical response

In all studies, patients treated with tocilizumab 8 mg/kg had statistically significant higher ACR 20, 50, 70 response rates at 6 months compared to control (Table 3). In study I, superiority of tocilizumab 8 mg/kg was demonstrated against the active comparator MTX.

The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race, number of prior treatments or disease status. Time to onset was rapid (as early as week 2) and the magnitude of response continued to improve with duration of treatment. Continued durable responses were seen for over 3 years in the ongoing open label extension studies I-V.

In patients treated with tocilizumab 8 mg/kg, significant improvements were noted on all individual components of the ACR response including: tender and swollen joint counts; patients and physician global assessment; disability index scores; pain assessment and CRP compared to patients receiving placebo plus MTX or other DMARDs in all studies.

Patients in studies I – V had a mean Disease Activity Score (DAS28) of 6.5–6.8 at baseline. Significant reduction in DAS28 from baseline (mean improvement) of 3.1–3.4 were observed in tocilizumab-treated patients compared to control patients (1.3–2.1). The proportion of patients achieving a DAS28 clinical remission ($\text{DAS28} < 2.6$) was significantly higher in patients receiving tocilizumab (28–34%) compared to 1–12% of control patients at 24 weeks. In study II, 65% of patients achieved a $\text{DAS28} < 2.6$ at week 104 compared to 48% at 52 weeks and 33% of patients at week 24.

In a pooled analysis of studies II, III and IV, the proportion of patients achieving an ACR 20, 50 and 70 response was significantly higher (59% vs. 50%, 37% vs. 27%, 18% vs. 11%, respectively) in the tocilizumab 8 mg/kg plus DMARD vs. the tocilizumab 4 mg/kg plus DMARD group ($p < 0.03$). Similarly the proportion of patients achieving a DAS28 remission ($\text{DAS28} < 2.6$) was significantly higher (31% vs. 16% respectively) in patients receiving tocilizumab 8 mg/kg plus DMARD than in patients receiving tocilizumab 4 mg/kg plus DMARD ($p < 0.0001$).

Table 3. ACR responses in placebo-/MTX-/DMARDs-controlled studies (% 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	PBO + MTX	TCZ 8 mg/kg + MTX	PBO + MTX	TCZ 8 mg/kg + DMARD	PBO + DMARD	TCZ 8 mg/kg + MTX	PBO + MTX
	N = 286	N = 284	N = 398	N = 393	N = 205	N = 204	N = 803	N = 413	N = 170	N = 158
ACR 20										
24	70%** *	52%	56%** *	27%	59%** *	26%	61%***	24%	50%***	10%
52			56%** *	25%						
ACR 50										
24	44%**	33%	32%***	10%	44%** *	11%	38%***	9%	29%** *	4%
52			36%***	10%						
ACR 70										
24	28%**	15%	13%***	2%	22%** *	2%	21%***	3%	12%**	1%
52			20%***	4%						

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

Major Clinical Response

After 2 years of treatment with tocilizumab plus MTX, 14% of patients achieved a major clinical response (maintenance of an ACR70 response for 24 weeks or more).

Radiographic response

In Study II, in patients with an inadequate response to MTX, inhibition of structural joint damage was assessed radiographically and expressed as change in modified Sharp score and its components, the erosion score and joint space narrowing score. Inhibition of joint structural damage was shown with significantly less radiographic progression in patients receiving tocilizumab compared to control (Table 4).

In the open-label extension of Study II the inhibition of progression of structural joint damage in tocilizumab plus MTX-treated patients was maintained in the second year of treatment. The mean change from baseline at week 104 in total Sharp-Genant score was significantly lower for patients randomised to tocilizumab 8 mg/kg plus MTX ($p < 0.0001$) compared with patients who were randomised to placebo plus MTX.

Table 4. Radiographic mean changes over 52 weeks in Study II

	PBO + MTX (+ TCZ from week 24) N = 393	TCZ 8 mg/kg + MTX N = 398
Total Sharp-Genant score	1.13	0.29*
Erosion score	0.71	0.17*
JSN score	0.42	0.12**

PBO - Placebo
MTX - Methotrexate
TCZ - Tocilizumab
JSN - Joint space narrowing
* - $p \leq 0.0001$, TCZ vs. PBO + MTX
** - $p < 0.005$, TCZ vs. PBO + MTX

Following 1 year of treatment with tocilizumab plus MTX, 85% of patients (n=348) had no progression of structural joint damage, as defined by a change in the Total Sharp Score of zero or less, compared with 67% of placebo plus MTX-treated patients (n=290) ($p \leq 0.001$). This remained consistent following 2 years of treatment (83%; n=353). Ninety three percent (93%; n=271) of patients had no progression between week 52 and week 104.

Health-related and quality of life outcomes

Tocilizumab-treated patients reported an improvement in all patient-reported outcomes (Health Assessment Questionnaire Disability Index - HAQ-DI), Short Form-36 and Functional Assessment of Chronic Illness Therapy questionnaires. Statistically significant improvements in HAQ-DI scores were observed in patients treated with RoActemra compared with patients treated with DMARDs. During the open-label period of Study II, the improvement in physical function has been maintained for up to 2 years. At Week 52, the mean change in HAQ-DI was -0.58 in the tocilizumab 8 mg/kg plus MTX group compared with -0.39 in the placebo + MTX group. The mean change in HAQ-DI was maintained at Week 104 in the tocilizumab 8 mg/kg plus MTX group (-0.61).

Haemoglobin levels

Statistically significant improvements in haemoglobin levels were observed with tocilizumab compared with DMARDs ($p < 0.0001$) at week 24. Mean haemoglobin levels increased by week 2 and remained within normal range through to week 24.

Tocilizumab versus adalimumab in monotherapy

Study VI (WA19924), a 24 week double-blinded study that compared tocilizumab monotherapy with adalimumab monotherapy, evaluated 326 patients with RA who were intolerant of MTX or where continued treatment with MTX was considered inappropriate (including MTX inadequate responders). Patients in the tocilizumab arm received an intravenous (IV) infusion of tocilizumab (8 mg/kg) every 4 weeks (q4w) and a subcutaneous (SC) placebo injection every 2 weeks (q2w). Patients in the adalimumab arm received an adalimumab SC injection (40 mg) q2w plus an IV placebo infusion q4w. A statistically significant superior treatment effect was seen in favour of tocilizumab over adalimumab in control of disease activity from baseline to week 24 for the primary endpoint of change in DAS28 and for all secondary endpoints (Table 5).

Table 5: Efficacy Results for Study VI (WA19924)

Table 3: Efficacy Results for Study 11 (N=1924)			
	ADA + Placebo (IV) N = 162	TCZ + Placebo (SC) N = 163	p-value ^(a)
Primary Endpoint - Mean Change from baseline at Week 24			
DAS28 (adjusted mean)	-1.8	-3.3	
Difference in adjusted mean (95% CI)	-1.5 (-1.8, -1.1)		<0.0001
Secondary Endpoints - Percentage of Responders at Week 24 ^(b)			
DAS28 < 2.6, n (%)	17 (10.5)	65 (39.9)	<0.0001
DAS28 ≤ 3.2, n (%)	32 (19.8)	84 (51.5)	<0.0001
ACR20 response, n (%)	80 (49.4)	106 (65.0)	0.0038
ACR50 response, n (%)	45 (27.8)	77 (47.2)	0.0002
ACR70 response, n (%)	29 (17.9)	53 (32.5)	0.0023

^ap value is adjusted for region and duration of RA for all endpoints and additionally baseline value for all continuous endpoints.

^b Non-responder Imputation used for missing data. Multiplicity controlled using Bonferroni-Holm Procedure

The overall clinical adverse event profile was similar between tocilizumab and adalimumab. The proportion of patients with serious adverse events was balanced between the treatment groups (tocilizumab 11.7% vs. adalimumab 9.9%). The types of adverse drug reactions in the tocilizumab arm were consistent with the known safety profile of tocilizumab and adverse drug reactions were reported at a similar frequency compared with Table 1. A higher incidence of infections and infestations was

reported in the tocilizumab arm (48% vs. 42%), with no difference in the incidence of serious infections (3.1%). Both study treatments induced the same pattern of changes in laboratory safety parameters (decreases in neutrophil and platelet counts, increases in ALT, AST and lipids), however, the magnitude of change and the frequency of marked abnormalities was higher with tocilizumab compared with adalimumab. Four (2.5%) patients in the tocilizumab arm and two (1.2%) patients in the adalimumab arm experienced CTC grade 3 or 4 neutrophil count decreases. Eleven (6.8%) patients in the tocilizumab arm and five (3.1%) patients in the adalimumab arm experienced ALT increases of CTC grade 2 or higher. The mean LDL increase from baseline was 0.64 mmol/L (25 mg/dL) for patients in the tocilizumab arm and 0.19 mmol/L (7 mg/dL) for patients in the adalimumab arm. The safety observed in the tocilizumab arm was consistent with the known safety profile of tocilizumab and no new or unexpected adverse drug reactions were observed (see Table 1).

MTX naïve, Early RA

Study VII (WA19926), a 2 year study with the planned primary analysis at week 52 evaluated 1162 MTX-naïve adult patients with moderate to severe, active early RA (mean disease duration ≤ 6 months). Approximately 20% of patients had received prior treatment with DMARDs other than MTX. This study evaluated the efficacy of IV tocilizumab 4 or 8 mg/kg every 4 weeks/MTX combination therapy, IV tocilizumab 8 mg/kg monotherapy and MTX monotherapy in reducing the signs and symptoms and rate of progression of joint damage for 104 weeks. The primary endpoint was the proportion of patients achieving DAS28 remission ($\text{DAS28} < 2.6$) at week 24. A significantly higher proportion of patients in the tocilizumab 8 mg/kg + MTX and tocilizumab monotherapy groups met the primary endpoint compared with MTX alone. The tocilizumab 8 mg/kg + MTX group also showed statistically significant results across the key secondary endpoints. Numerically greater responses compared with MTX alone were observed in the tocilizumab 8 mg/kg monotherapy group in all secondary endpoints, including radiographic endpoints. In this study, ACR/EULAR remission (Boolean and Index) were also analysed as pre-specified exploratory endpoints, with higher responses observed in the tocilizumab groups. The results from study VII are shown in Table 6.

Table 6: Efficacy Results for Study VII (WAI9926) on MTX-naïve, early RA patients

		TCZ 8 mg/kg + MTX N=290	TCZ 8 mg/kg + placebo N=292	TCZ 4 mg/kg + MTX N=288	Placebo + MTX N=287
Primary Endpoint					
DAS28 Remission					
Week 24	n (%)	130 (44.8)***	113 (38.7)***	92 (31.9)	43 (15.0)
Key Secondary Endpoints					
DAS 28 remission					
Week 52	n (%)	142 (49.0)***	115 (39.4)	98 (34.0)	56 (19.5)
ACR					
Week 24	ACR20, n (%)	216 (74.5)*	205 (70.2)	212 (73.6)	187 (65.2)
	ACR50, n (%)	165 (56.9)**	139 (47.6)	138 (47.9)	124 (43.2)
	ACR70, n (%)	112 (38.6)**	88 (30.1)	100 (34.7)	73 (25.4)
Week 52	ACR20, n (%)	195 (67.2)*	184 (63.0)	181 (62.8)	164 (57.1)
	ACR50, n (%)	162 (55.9)**	144 (49.3)	151 (52.4)	117 (40.8)
	ACR70, n (%)	125 (43.1)**	105 (36.0)	107 (37.2)	83 (28.9)
HAQ-DI (adjusted mean change from baseline)					
Week 52		-0.81*	-0.67	-0.75	-0.64
Radiographic Endpoints (mean change from baseline)					
Week 52	mTSS	0.08***	0.26	0.42	1.14
	Erosion Score	0.05**	0.15	0.25	0.63
	JSN	0.03	0.11	0.17	0.51
Radiographic Non-Progression n (%) (change from baseline in mTSS of ≤0)		226 (83) [‡]	226 (82) [‡]	211 (79)	194 (73)
Exploratory Endpoints					
Week 24: ACR/EULAR Boolean Remission, n (%)		47 (18.4) [‡]	38 (14.2)	43 (16.7) [‡]	25 (10.0)
ACR/EULAR Index Remission, n (%)		73 (28.5) [‡]	60 (22.6)	58 (22.6)	41 (16.4)
Week 52: ACR/EULAR Boolean Remission, n (%)		59 (25.7) [‡]	43 (18.7)	48 (21.1)	34 (15.5)
ACR/EULAR Index Remission, n (%)		83 (36.1) [‡]	69 (30.0)	66 (29.3)	49 (22.4)

mTSS - modified Total Sharp Score

JSN - Joint space narrowing

All efficacy comparisons vs Placebo + MTX. ***p≤0.0001; **p<0.001; *p<0.05;

[‡]p-value < 0.05 vs. Placebo + MTX, but endpoint was exploratory (not included in the hierarchy of statistical testing and has therefore not been controlled for multiplicity)

Paediatric population

sJIA Patients

Clinical efficacy

The efficacy of tocilizumab for the treatment of active sJIA was assessed in a 12 week randomised, double blind, placebo-controlled, parallel group, two arm study. Patients included in the trial had a total disease duration of at least 6 months and active disease but were not experiencing an acute flare requiring corticosteroid doses of more than 0.5 mg/kg prednisone equivalent. Efficacy for the treatment of macrophage activation syndrome has not been investigated.

Patients (treated with or without MTX) were randomised (tocilizumab:placebo = 2:1) to one of two treatment groups, 75 patients received tocilizumab infusions every two weeks, either 8 mg/kg for patients ≥ 30 kg or 12 mg/kg for patients < 30 kg and 37 patients were assigned to receiving placebo

infusions every two weeks. Corticosteroid tapering was permitted from week six for patients who achieved a JIA ACR70 response. After 12 weeks or at the time of escape, due to disease worsening, patients were treated in the open label phase at weight appropriate dosing.

Clinical response

The primary endpoint was the proportion of patients with at least 30% improvement in the JIA ACR core set (JIA ACR30 response) at week 12 and absence of fever (no temperature recording $\geq 37.5^{\circ}\text{C}$ in the preceding 7 days). Eighty five percent (64/75) of tocilizumab treated patients and 24.3% (9/37) of placebo treated patients achieved this endpoint. These proportions were highly significantly different ($p<0.0001$).

The percent of patients achieving JIA ACR 30, 50, 70 and 90 responses are shown in Table 7.

Table 7. JIA ACR response rates at week 12 (% patients)

Response Rate	Tocilizumab N = 75	Placebo N = 37
JIA ACR 30	90.7% ¹	24.3%
JIA ACR 50	85.3% ¹	10.8%
JIA ACR 70	70.7% ¹	8.1%
JIA ACR 90	37.3% ¹	5.4%

¹ $p<0.0001$, tocilizumab vs. placebo

Systemic Effects

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

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

Corticosteroid Tapering

Patients achieving a JIA ACR70 response were permitted corticosteroid dose reduction. Seventeen (24%) tocilizumab treated patients versus 1 (3%) placebo patient were able to reduce their dose of corticosteroid 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 tocilizumab 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

Fifty out of seventy five (67%) tocilizumab treated patients had a haemoglobin $< \text{LLN}$ baseline. Forty (80%) of these patients had an increase in their haemoglobin to within the normal range at week 12, in comparison to 2 out of 29 (7%) of placebo treated patients with haemoglobin at baseline ($p<0.0001$).

pJIA Patients

Clinical efficacy

The efficacy of tocilizumab was assessed in a three-part study WA19977 including an open-label extension in children with active pJIA. Part I consisted of a 16-week active tocilizumab treatment lead-in period ($n=188$) followed by Part II, a 24-week randomized double-blind placebo-controlled withdrawal period ($n=163$), followed by Part III, a 64-week open-label period. In Part I, eligible patients ≥ 30 kg received tocilizumab at 8 mg/kg IV every 4 weeks for 4 doses. Patients < 30 kg were randomized 1:1 to receive either tocilizumab 8 mg/kg or 10 mg/kg IV every 4 weeks for 4 doses. Patients who completed Part I of the study and achieved at least a JIA ACR30 response at week 16

compared to baseline were eligible to enter the blinded withdrawal period (Part II) of the study. In Part II, patients were randomized to tocilizumab (same dose received in Part I) or placebo in a 1:1 ratio, stratified by concurrent MTX use and concurrent corticosteroid use. Each patient continued in Part II of the study until Week 40 or until the patient satisfied JIA ACR30 flare criteria (relative to Week 16) and qualified for escape to tocilizumab therapy (same dose received in Part I).

Clinical response

The primary endpoint was the proportion of patients with a JIA ACR30 flare at week 40 relative to week 16. Forty eight percent (48.1%, 39/81) of the patients treated with placebo flared compared with 25.6% (21/82) of tocilizumab treated patients. These proportions were statistically significantly different ($p=0.0024$).

At the conclusion of Part I, JIA ACR 30/50/70/90 responses were 89.4%, 83.0%, 62.2%, and 26.1%, respectively.

During the withdrawal phase (Part II), the percentage of patients achieving JIA ACR 30, 50, and 70 responses at Week 40 relative to baseline are shown in Table 8. In this statistical analysis, patients who flared (and escaped to TCZ) during Part II or who withdrew, were classified as non-responders. An additional analyses of JIA ACR responses, considering observed data at Week 40, regardless of flare status, showed that by Week 40, 95.1% of patients who had received continuous TCZ therapy, had achieved JIA ACR30 or higher.

Table 8. JIA ACR Response Rates at Week 40 Relative to baseline (Percentage of Patients)

Response Rate	Tocilizumab N=82	Placebo N=81
ACR 30	74.4%*	54.3%*
ACR 50	73.2%*	51.9%*
ACR 70	64.6%*	42.0%*

* $p<0.01$, tocilizumab vs. placebo

The number of active joints was significantly reduced compared to baseline in patients receiving tocilizumab compared to placebo (adjusted mean changes of -14.3 vs -11.4, $p=0.0435$). The physician's global assessment of disease activity, as measured on a 0-100 mm scale, showed a greater reduction in disease activity for tocilizumab compared to placebo (adjusted mean changes of -45.2 mm vs -35.2 mm, $p=0.0031$).

The adjusted mean change in the pain VAS after 40 weeks of tocilizumab treatment was 32.4 mm on a 0-100 mm scale compared to a reduction of 22.3 mm for placebo patients (highly statistically significant; $p=0.0076$).

The ACR response rates were numerically lower for patients with prior biologic treatment as shown in Table 9 below.

Table 9. Number and Proportion of Patients with a JIA ACR30 Flare and Proportion of Patients with JIA ACR30/50/70/90 Responses at Week 40, by Previous Biologic Use (ITT Population - Study Part II)

	Placebo		All TCZ	
Biologic Use	Yes (N = 23)	No (N = 58)	Yes (N = 27)	No (N = 55)
JIA ACR30 Flare	18 (78.3)	21 (36.2)	12 (44.4)	9 (16.4)
JIA ACR30 Response	6 (26.1)	38 (65.5)	15 (55.6)	46 (83.6)
JIA ACR50 Response	5 (21.7)	37 (63.8)	14 (51.9)	46 (83.6)
JIA ACR70 Response	2 (8.7)	32 (55.2)	13 (48.1)	40 (72.7)
JIA ACR90 Response	2 (8.7)	17 (29.3)	5 (18.5)	32 (58.2)

Patients randomized to tocilizumab had fewer ACR30 flares and higher overall ACR responses than patients receiving placebo regardless of a history of prior biologic use.

The European Medicines Agency has waived the obligation to submit the results of studies with RoActemra in all subsets of the paediatric population in rheumatoid arthritis and has deferred the obligation to submit the results of studies with RoActemra in one or more subsets of the paediatric population in juvenile idiopathic arthritis. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

RA Patients

Intravenous use

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 3552 RA patients treated with a one-hour infusion of 4 or 8 mg/kg tocilizumab every 4 weeks for 24 weeks or with 162 mg tocilizumab given subcutaneously either once a week or every other week for 24 weeks.

The following parameters (predicted mean \pm SD) were estimated for a dose of 8 mg/kg tocilizumab given every 4 weeks: steady-state area under curve (AUC) = 38000 ± 13000 h μ g/ml, trough concentration (C_{\min}) = 15.9 ± 13.1 μ g/ml and maximum concentration (C_{\max}) = 182 ± 50.4 μ g/ml, and the accumulation ratios for AUC and C_{\max} were small, 1.32 and 1.09, respectively. The accumulation ratio was higher for C_{\min} (2.49), which was expected based on the non-linear clearance contribution at lower concentrations. Steady-state was reached following the first administration for C_{\max} and after 8 and 20 weeks for AUC and C_{\min} , respectively. Tocilizumab AUC, C_{\min} and C_{\max} increased with increase of body weight. At body weight ≥ 100 kg, the predicted mean (\pm SD) steady-state AUC, C_{\min} and C_{\max} of tocilizumab were 50000 ± 16800 μ g·h/mL, 24.4 ± 17.5 μ g/mL, and 226 ± 50.3 μ g/mL, respectively, which are higher than mean exposure values for the patient population (i.e. all body weights) reported above. The dose-response curve for tocilizumab flattens at higher exposure, resulting in smaller efficacy gains for each incremental increase in tocilizumab concentration such that clinically meaningful increases in efficacy were not demonstrated in patients treated with > 800 mg of tocilizumab. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended (see section 4.2).

Distribution

In RA patients the central volume of distribution was 3.72, the peripheral volume of distribution was 3.35 resulting in a volume of distribution at steady state of 7.07.

Elimination

Following intravenous administration, tocilizumab undergoes biphasic elimination from the circulation. The total clearance of tocilizumab was concentration-dependent and is the sum of the linear and non-linear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 9.5 ml/h. The concentration-dependent non-linear clearance plays a

major role at low tocilizumab concentrations. Once the non-linear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.

The $t_{1/2}$ of tocilizumab was concentration-dependent. At steady-state following a dose of 8 mg/kg every 4 weeks, the effective $t_{1/2}$ decreased with decreasing concentrations within a dosing interval from 18 days to 6 days.

Linearity

Pharmacokinetic parameters of tocilizumab did not change with time. A more than dose-proportional increase in the AUC and C_{min} was observed for doses of 4 and 8 mg/kg every 4 weeks. C_{max} increased dose-proportionally. At steady-state, predicted AUC and C_{min} were 3.2 and 30 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively.

Special populations

Renal impairment: No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab has been conducted. Most of the patients in the population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (creatinine clearance based on Cockcroft-Gault < 80 ml/min and ≥ 50 ml/min) did not impact the pharmacokinetics of tocilizumab.

Hepatic impairment: No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab has been conducted.

Age, gender and ethnicity: Population pharmacokinetic analyses in RA patients, showed that age, gender and ethnic origin did not affect the pharmacokinetics of tocilizumab.

sJIA Patients:

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 75 sJIA patients treated with 8 mg/kg (patients with a body weight ≥ 30 kg) or 12 mg/kg (patients with a body weight < 30 kg), given every 2 weeks. The predicted mean (\pm SD) AUC_{2weeks} , C_{max} and C_{min} of tocilizumab were 32200 ± 9960 $\mu\text{g}\cdot\text{h/mL}$, 245 ± 57.2 $\mu\text{g/mL}$ and 57.5 ± 23.3 $\mu\text{g/mL}$, respectively. The accumulation ratio for C_{min} (week 12 / week 2) was 3.2 ± 1.3 . The tocilizumab C_{min} was stabilized after week 12. Mean predicted tocilizumab exposure parameters were similar between the two body weight groups.

In sJIA patients, the central volume of distribution was 35 ml/kg and the peripheral volume of distribution was 60 ml/kg resulting in a volume of distribution at a steady state of 95 ml/kg. The linear clearance estimated as a parameter in the population pharmacokinetic analysis, was 0.142 ml/hr/kg.

The half life of tocilizumab in sJIA patients is up to 23 days for the two body weight categories (8 mg/kg for body weight ≥ 30 kg or 12 mg/kg for body weight < 30 kg) at week 12.

pJIA Patients:

The pharmacokinetics of tocilizumab was determined using a population pharmacokinetic analysis on a database composed of 188 patients with pJIA.

The following parameters are valid for a dose of 8 mg/kg tocilizumab (patients with a body weight ≥ 30 kg) given every 4 weeks. The predicted mean (\pm SD) AUC_{4weeks} , C_{max} and C_{min} of tocilizumab were 29500 ± 8660 $\mu\text{g}\cdot\text{hr/mL}$, 182 ± 37 $\mu\text{g/mL}$ and 7.49 ± 8.20 $\mu\text{g/mL}$, respectively.

The following parameters are valid for a dose of 10 mg/kg tocilizumab (patients with a body weight < 30 kg) given every 4 weeks. The predicted mean (\pm SD) AUC_{4weeks} , C_{max} and C_{min} of tocilizumab were 23200 ± 6100 $\mu\text{g}\cdot\text{hr/mL}$, 175 ± 32 $\mu\text{g/mL}$ and 2.35 ± 3.59 $\mu\text{g/mL}$, respectively.

The accumulation ratios were 1.05 and 1.16 for AUC_{4weeks} , and 1.43 and 2.22 for C_{min} for 10 mg/kg (body weight < 30 kg) and 8 mg/kg (body weight ≥ 30 kg) doses, respectively. No accumulation for C_{max} was observed.

In pJIA patients, the central volume of distribution was 50 ml/kg, the peripheral volume of distribution was 53 ml/kg, resulting in a volume of distribution at steady state of 103 ml/kg. The linear clearance estimated as a parameter in the population pharmacokinetic analysis was 0.146 ml/hr/kg.

The half life of tocilizumab in pJIA patients is up to 16 days for the two body weight categories (8 mg/kg for body weight \geq 30 kg or 10 mg/kg for body weight < 30 kg) during a dosing interval at steady state.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Carcinogenicity studies were not performed because IgG1 monoclonal antibodies are not deemed to have intrinsic carcinogenic potential.

Available non-clinical data demonstrated the effect of IL-6 on malignant progression and apoptosis resistance to various cancer types. This data does not suggest a relevant risk for cancer initiation and progression under tocilizumab treatment. Additionally, proliferative lesions were not observed in a 6-month chronic toxicity study in cynomolgus monkeys or in IL-6 deficient mice.

Available non-clinical data do not suggest an effect on fertility under tocilizumab treatment. Effects on endocrine active and reproductive system organs were not observed in a chronic cynomolgus monkey toxicity study and reproductive performance was not affected in IL-6 deficient mice. Tocilizumab administered to cynomolgus monkeys during early gestation, was observed to have no direct or indirect harmful effect on pregnancy or embryonal-foetal development. However, a slight increase in abortion/embryonal-foetal death was observed with high systemic exposure ($> 100 \times$ human exposure) in the 50 mg/kg/day high-dose group compared to placebo and other low-dose groups. Although IL-6 does not seem to be a critical cytokine for foetal growth or the immunological control of the maternal/foetal interface, a relation of this finding to tocilizumab cannot be excluded.

Treatment with a murine analogue did not exert toxicity in juvenile mice. In particular, there was no impairment of skeletal growth, immune function and sexual maturation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Polysorbate 80
Disodium phosphate dodecahydrate
Sodium dihydrogen phosphate dihydrate
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial: 30 months

Diluted product: After dilution, the prepared solution for infusion is physically and chemically stable in sodium chloride 9 mg/ml (0.9%) solution for injection at 30°C for 24 hours.

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in use storage times and conditions 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.

6.4 Special precautions for storage

Store vials in a refrigerator (2°C–8°C). Do not freeze.

Keep the vial(s) in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product see section 6.3.

6.5 Nature and contents of container

RoActemra is supplied in a vial (type I glass) with a stopper (butyl rubber) containing 4 ml, 10 ml or 20 ml concentrate. Pack sizes of 1 and 4 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for dilution prior to administration

Parenteral medicinal products should be inspected visually for particulate matter or discolouration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted.

RA Patients

Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection from a 100 ml infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (0.4 ml/kg) should be withdrawn from the vial and placed in the 100 ml infusion bag. This should be a final volume of 100 ml. To mix the solution, gently invert the infusion bag to avoid foaming.

Use in the paediatric population

sJIA and pJIA Patients ≥ 30 kg

Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection from a 100 ml infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.4 ml/kg**) should be withdrawn from the vial and placed in the 100 ml infusion bag. This should be a final volume of 100 ml. To mix the solution, gently invert the infusion bag to avoid foaming.

sJIA Patients < 30 kg

Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection from a 50 ml infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.6 ml/kg**) should be withdrawn from the vial and placed in the 50 ml infusion bag. This should be a final volume of 50 ml. To mix the solution, gently invert the infusion bag to avoid foaming.

pJIA Patients < 30 kg

Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection from a 50 ml infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.5 ml/kg**) should be withdrawn from the vial and placed in the 50 ml infusion bag. This should be a final volume of 50 ml. To mix the solution, gently invert the infusion bag to avoid foaming.

RoActemra is for single-use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/001
EU/1/08/492/002
EU/1/08/492/003
EU/1/08/492/004
EU/1/08/492/005
EU/1/08/492/006

9. DATE OF FIRST AUTHORISATION/DATE OF LATEST RENEWAL

Date of first authorisation: 16 January 2009

Date of last renewal: 25 July 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu/>.

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 162 mg solution for injection in pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 162 mg of tocilizumab in 0.9 ml.

Tocilizumab is a recombinant humanized, anti-human monoclonal antibody of the immunoglobulin G1 (IgG1) sub-class directed against soluble and membrane-bound interleukin 6 receptors.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

A colourless to slightly yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RoActemra, in combination with methotrexate (MTX), is indicated for

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
- the treatment of moderate to severe active 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 methotrexate.

RoActemra is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients.

4.2 Posology and method of administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA and / or GCA. All patients treated with RoActemra should be given the Patient Alert Card. Suitability of the patient for subcutaneous home use should be assessed and patients should be instructed to inform a healthcare professional if they experience symptoms of an allergic reaction. Patients should seek immediate medical attention if they develop symptoms of serious allergic reactions (see section 4.4).

Posology

RoActemra subcutaneous formulation is not intended for intravenous administration.

RA

The recommended posology is subcutaneous 162 mg once every week.

Limited information is available regarding switching patients from RoActemra intravenous formulation to RoActemra subcutaneous fixed dose-formulation. The once every week dosing interval should be followed.

Patients transitioning from intravenous to subcutaneous formulation should administer their first subcutaneous dose instead of the next scheduled intravenous dose under the supervision of a qualified healthcare professional.

GCA

The recommended posology is subcutaneous 162 mg once every week in combination with a tapering course of glucocorticoids. RoActemra can be used alone following discontinuation of glucocorticoids. RoActemra monotherapy should not be used for the treatment of acute relapses (see 4.4).

Based upon the chronic nature of GCA, treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice.

RA and GCA

Dose adjustments due to laboratory abnormalities (see section 4.4).

- Liver enzyme abnormalities

Laboratory Value	Action
> 1 to 3 x Upper Limit of Normal (ULN)	Dose modify concomitant DMARDs (RA) or immunomodulatory agents (GCA) if appropriate. For persistent increases in this range, reduce RoActemra dose frequency to every other week injection or interrupt RoActemra until alanine aminotransferase (ALT) or aspartate aminotransferase (AST) have normalised. Restart with weekly or every other week injection, as clinically appropriate.
> 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 (confirmed by repeat testing, see 4.4.), discontinue RoActemra.
> 5 x ULN	Discontinue RoActemra.

- Low absolute neutrophil count (ANC)

In patients not previously treated with RoActemra, initiation is not recommended in patients with an absolute neutrophil count (ANC) below $2 \times 10^9/L$

Laboratory Value (cells x 10 ⁹ /L)	Action
ANC > 1	Maintain dose.
ANC 0.5 to 1	Interrupt RoActemra dosing. When ANC increases > 1 x 10 ⁹ /L resume RoActemra dosing every other week and increase to every week injection, as clinically appropriate.
ANC < 0.5	Discontinue RoActemra.

- Low platelet count

Laboratory Value (cells x 10 ³ /μL)	Action
50 to 100	Interrupt RoActemra dosing. When platelet count > 100 x 10 ³ /μL resume RoActemra dosing every other week and increase to every week injection as clinically appropriate.
< 50	Discontinue RoActemra.

Missed dose

If a patient misses a subcutaneous weekly injection of RoActemra within 7 days of the scheduled dose, he/she should be instructed to take the missed dose on the next scheduled day. If a patient misses a subcutaneous once every other week injection of RoActemra within 7 days of the scheduled dose, he/she should be instructed to take the missed dose immediately and the next dose on the next scheduled day.

Special populations

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 or moderate renal impairment. RoActemra has not been studied in patients with severe renal impairment (see section 5.2). 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.

Paediatric patients

The safety and efficacy of RoActemra subcutaneous formulation in children from birth to less than 18 years have not been established. No data are available.

Method of administration

RoActemra is for subcutaneous use.

After proper training in injection technique, patients may self-inject with RoActemra if their physician determines that it is appropriate. The total content (0.9 ml) of the pre-filled syringe should be administered as a subcutaneous injection. The recommended injection sites (abdomen, thigh and upper arm) should be rotated and injections should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

The pre-filled syringe should not be shaken.

Comprehensive instructions for the administration of RoActemra in a pre-filled syringe are given in the package leaflet, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including RoActemra (see section 4.8, Undesirable effects). RoActemra treatment must not be initiated in patients with active infections (see section 4.3). Administration of RoActemra should be interrupted if a patient develops a serious infection until the infection is controlled (see section 4.8). Healthcare professionals should exercise caution when considering the use of RoActemra in patients with a history of recurring or chronic infections or with underlying conditions (e.g.) diverticulitis, diabetes and interstitial lung disease which may predispose patients to infections.

Vigilance for the timely detection of serious infection is recommended for patients receiving immunosuppressive agents such as RoActemra for moderate to severe RA or GCA as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute phase reactants. The effects of tocilizumab on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients should be instructed to contact their healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

Tuberculosis

As recommended for other biological treatments, all patients should be screened for latent tuberculosis (TB) infection prior to starting RoActemra therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating RoActemra. Prescribers are reminded of the risk of false negative tuberculin skin and interferon-gamma TB blood test results, especially in patients who are severely ill or immunocompromised.

Patients should be advised to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade (fever) suggestive of a tuberculosis infection occur during or after therapy with RoActemra.

Viral reactivation

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

Complications of diverticulitis

Events of diverticular perforations as complications of diverticulitis have been reported uncommonly in patients treated with RoActemra (see section 4.8). RoActemra should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis which can be associated with gastrointestinal perforation.

Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylaxis have been reported in association with RoActemra (see section 4.8). Such reactions may be more severe, and potentially fatal in patients who have experienced hypersensitivity reactions during previous treatment with tocilizumab even if they have received premedication with steroids and antihistamines. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of RoActemra should be stopped immediately, appropriate therapy initiated and tocilizumab 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 (see sections 4.2 and 4.8).

Hepatic transaminase elevations

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 (see section 4.8). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with RoActemra. When clinically indicated, other liver function tests including bilirubin should be considered.

Caution should be exercised when considering initiation of RoActemra treatment in patients with elevated ALT or AST $> 1.5 \times \text{ULN}$. In patients with baseline ALT or AST $> 5 \times \text{ULN}$, treatment is not recommended.

In RA and GCA patients, 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 recommended modifications based on transaminases see section 4.2. For ALT or AST elevations $> 3\text{--}5 \times \text{ULN}$, RoActemra treatment should be interrupted.

Haematological abnormalities

Decreases in neutrophil and platelet counts have occurred following treatment with tocilizumab 8 mg/kg in combination with MTX (see section 4.8). There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist.

In patients not previously treated with RoActemra, initiation is not recommended in patients with an ANC below $2 \times 10^9/\text{L}$. Caution should be exercised when considering initiation of RoActemra treatment in patients with a low platelet count (i.e. platelet count below $100 \times 10^3/\mu\text{L}$). In patients who develop an ANC $< 0.5 \times 10^9/\text{L}$ or a platelet count $< 50 \times 10^3/\mu\text{L}$, continued treatment is not recommended.

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 RA and GCA patients, neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. For recommended dose modifications based on ANC and platelet counts, see section 4.2.

Lipid parameters

Elevations in lipid parameters including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were observed in patients treated with tocilizumab (see section 4.8). In the majority of patients, there was no increase in atherogenic indices, and elevations in total cholesterol responded to treatment with lipid lowering agents.

In RA and GCA patients, assessment of lipid parameters should be performed 4 to 8 weeks following initiation of RoActemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

Neurological disorders

Physicians should be vigilant for symptoms potentially indicative of new-onset central demyelinating disorders. The potential for central demyelination with RoActemra is currently unknown.

Malignancy

The risk of malignancy is increased in patients with RA. Immunomodulatory medicinal products may increase the risk of malignancy.

Vaccinations

Live and live attenuated vaccines should not be given concurrently with RoActemra as clinical safety has not been established. In a randomized open-label study, adult RA patients treated with RoActemra and MTX were able to mount an effective response to both the 23-valent pneumococcal polysaccharide and tetanus toxoid vaccines which was comparable to the response seen in patients on MTX only. It is recommended that all patients particularly elderly 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

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

Combination with TNF antagonists

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

GCA

RoActemra monotherapy should not be used for the treatment of acute relapses as efficacy in this setting has not been established. Glucocorticoids should be given according to medical judgement and practice guidelines.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Concomitant administration of a single dose of 10 mg/kg RoActemra with 10-25 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 in RA patients. In GCA patients, no effect of cumulative corticosteroid dose on RoActemra exposure was observed.

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 tocilizumab, to the level similar to, or slightly higher than, those observed in healthy subjects.

When starting or stopping therapy with tocilizumab, patients taking medicinal products which are individually adjusted and are metabolised via CYP450 3A4, 1A2 or 2C9 (e.g. methylprednisolone, dexamethasone, (with the possibility for oral glucocorticoid withdrawal syndrome), atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses may need to be increased to maintain therapeutic effect. Given its long elimination half-life ($t_{1/2}$), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

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 (see section 5.3). The potential risk for humans is unknown.

RoActemra should not be used during pregnancy unless clearly necessary.

Breast-feeding

It is unknown whether tocilizumab 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.

Fertility

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

4.7 Effects on ability to drive and use machines

RoActemra has a minor influence on the ability to drive and use machines (see section 4.8, dizziness).

4.8 Undesirable effects

Summary of the safety profile

The safety profile comes from 4158 patients exposed to RoActemra in clinical trials; the majority of these patients were participating in RA studies (n=4009), while the remaining experience comes from GCA (n=149) studies. The safety profile of RoActemra across these indications remains similar and undifferentiated.

The most commonly reported Adverse Drug Reactions (ADRs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

The most serious ADRs were serious infections, complications of diverticulitis, and hypersensitivity reactions.

Tabulated summary of adverse reactions

The ADRs listed in Table 1 are presented by system organ class and frequency categories, defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$) rare, ($\geq 1/10,000$ to $< 1/1,000$) or very rare ($< 1/10,000$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. Summary of ADRs occurring in patients treated with RoActemra.

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

* Includes elevations collected as part of routine laboratory monitoring (see text below)

RA

Intravenous use

The safety of RoActemra has been studied in 4 placebo-controlled studies (studies II, III, IV and V), 1 MTX-controlled study (study I) and their extension periods (see section 5.1).

The double-blind controlled period was 6 months in four studies (studies I, III, IV and V) and was up to 2 years in one study (study II). In the double-blind controlled studies, 774 patients received RoActemra 4 mg/kg in combination with MTX, 1870 patients received RoActemra 8 mg/kg in combination with MTX or other DMARDs and 288 patients received RoActemra 8 mg/kg monotherapy.

The long-term exposure population includes all patients who received at least one dose of RoActemra either in the double-blind control period or open label extension phase in the studies. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3296 for at least one year, 2806 received treatment for at least 2 years and 1222 for 3 years.

Description of selected adverse reactions

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, which may present with intrapulmonary or extrapulmonary disease, invasive pulmonary infections, including candidiasis, aspergillosis, coccidioidomycosis and pneumocystis jirovecii, pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported.

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.

Gastrointestinal perforation

During the 6-month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient years with tocilizumab 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.

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 tocilizumab 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 8/4,009 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 56 out of 4,009 patients (1.4%) treated with RoActemra during the controlled and open label clinical studies. These reactions were generally observed during the second to fifth infusions of tocilizumab (see section 4.4). Fatal anaphylaxis has been reported after marketing authorisation during treatment with intravenous RoActemra (see section 4.4).

Immunogenicity

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

Haematological abnormalities:

Neutrophils

In the 6-month controlled trials decreases in neutrophil counts below $1 \times 10^9/\text{L}$ 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 < $1 \times 10^9/\text{L}$ did so within 8 weeks after starting therapy. Decreases below $0.5 \times 10^9/\text{L}$ 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.

Platelets

In the 6-month controlled trials decreases in platelet counts below $100 \times 10^3/\mu\text{L}$ 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.

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 tocilizumab 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 tocilizumab plus DMARD patients, the majority of whom were discontinued permanently from tocilizumab 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 the upper limit of normal, collected as a routine laboratory parameter, is 6.2% in patients treated with 8 mg/kg RoActemra + DMARD. A total of 5.8% of patients experienced an elevation of indirect bilirubin of > 1 to 2 x ULN and 0.4% had an elevation of > 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 $\geq 6.2 \text{ mmol/L}$, with 15% experiencing a sustained increase in LDL to $\geq 4.1 \text{ mmol/L}$. 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 tocilizumab. Long-term safety evaluations are ongoing.

Skin Reactions

Very rare reports of Stevens-Johnson Syndrome have occurred in the post marketing setting.

Subcutaneous use

RA

The safety of subcutaneous RoActemra in RA includes a double-blind, controlled, multicenter study, SC-I. SC-I was a non-inferiority study that compared the efficacy and safety of RoActemra 162 mg administered every week versus 8 mg/kg intravenous in 1262 patients with RA. All patients received background non-biologic DMARD(s). The safety and immunogenicity observed for RoActemra administered subcutaneous was consistent with the known safety profile of intravenous RoActemra and no new or unexpected adverse drug reactions were observed (see Table 1). A higher frequency of injection site reactions was observed in the subcutaneous arms compared with placebo subcutaneous injections in the intravenous arms.

Injection site reactions

During the 6-month controlled period, in SC-I, the frequency of injection site reactions was 10.1% (64/631) and 2.4% (15/631) for the subcutaneous tocilizumab and the subcutaneous placebo (intravenous group) weekly injections, respectively. These injection site reactions (including erythema, pruritus, pain and haematoma) were mild to moderate in severity. The majority was resolved without any treatment and none necessitated drug discontinuation.

Immunogenicity

In SC-I, a total of 625 patients treated with RoActemra 162mg weekly were tested for anti-RoActemra antibodies in the 6 month controlled period. Five patients (0.8%) developed positive anti-RoActemra antibodies; of these, all developed neutralizing anti-RoActemra antibodies. One patient was tested positive for IgE isotype (0.2%).

In SC-II, a total of 434 patients treated with tocilizumab 162mg every other week were tested for anti-RoActemra antibodies in the 6 month controlled period. Seven patients (1.6%) developed positive antiRoActemra antibodies; of these, six (1.4%) developed neutralizing anti-RoActemra antibodies. Four patients were tested positive for IgE isotype (0.9%).

No correlation of antibody development to clinical response or adverse events was observed.

Haematological abnormalities:

Neutrophils

During routine laboratory monitoring in the tocilizumab 6 month controlled clinical trial SC-I, a decrease in neutrophil count below $1 \times 10^9/L$ occurred in 2.9% of patients on the subcutaneous weekly dose.

There was no clear relationship between decreases in neutrophils below $1 \times 10^9/L$ and the occurrence of serious infections.

Platelets

During routine laboratory monitoring in the tocilizumab 6 month clinical trial SC-I, none of the patients on the SC weekly dose had a decrease in platelet count to $\leq 50 \times 10^3 / \mu L$.

Hepatic transaminase elevations

During routine laboratory monitoring in the tocilizumab 6-month controlled clinical trial SC-I, elevation in ALT or AST $\geq 3 \times ULN$ occurred in 6.5% and 1.4% of patients, respectively on the subcutaneous weekly dose.

Lipid parameters

During routine laboratory monitoring in the RoActemra 6 month controlled clinical trial SC-I, 19% of patients experienced sustained elevations in total cholesterol $> 6.2 \text{ mmol/L}$ (240 mg/dl), with 9%

experiencing a sustained increase in LDL to ≥ 4.1 mmol/L (160 mg/dL) on the subcutaneous weekly dose.

Subcutaneous use

GCA

The safety of subcutaneous RoActemra has been studied in one Phase III study (WA28119) with 251 GCA patients. The total patient years duration in the RoActemra all exposure population was 138.5 patient years during the 12 month double blind, placebo controlled phase of the study. The overall safety profile observed in the RoActemra treatment groups was consistent with the known safety profile of RoActemra (see Table 1).

Infections

The rate of infection/serious infection events was balanced between the RoActemra weekly group (200.2/9.7 events per 100 patient years) vs. placebo plus 26 weeks prednisone taper (156.0/4.2 events per 100 patient years) and placebo plus 52 weeks taper (210.2/12.5 events per 100 patient years) groups.

Injection site reactions

In the RoActemra subcutaneous weekly group, a total of 6% (6/100) patients reported an adverse reaction occurring at the site of a subcutaneous injection. No injection site reaction was reported as a serious adverse event or required treatment discontinuation.

Immunogenicity

In the RoActemra subcutaneous weekly group, one patient (1.1%, 1/95) developed positive neutralizing anti-RoActemra antibodies, though not of the IgE isotype. This patient did not develop a hypersensitivity reaction or injection site reaction.

Haematological abnormalities:

Neutrophils

During routine laboratory monitoring in the Roactemra 12 month controlled clinical trial, a decrease in neutrophil count below 1×10^9 /L occurred in 4% of patients in the RoActemra subcutaneous weekly group. This was not observed in either of the placebo plus prednisone taper groups.

Platelets

During routine laboratory monitoring in the RoActemra 12 month controlled clinical trial, one patient (1%, 1/100) in the RoActemra subcutaneous weekly group had a single transient occurrence of decrease in platelet count to $<100 \times 10^3$ / μ L without associated bleeding events. A decrease in platelet count below 100×10^3 / μ L was not observed in either of the placebo plus prednisone taper groups.

Hepatic transaminase elevations

During routine laboratory monitoring in the RoActemra 12 month controlled clinical trial, elevation in ALT $\geq 3 \times$ ULN occurred in 3% of patients in the RoActemra subcutaneous weekly group compared to 2% in the placebo plus 52 week prednisone taper group and none in the placebo plus 26 week prednisone taper group. An elevation in AST > 3 ULN occurred in 1% of patients in the RoActemra subcutaneous weekly group, compared to no patients in either of the placebo plus prednisone taper groups.

Lipid parameters

During routine laboratory monitoring in the RoActemra 12 month controlled clinical trial, 34% of patients experienced sustained elevations in total cholesterol > 6.2 mmol/L (240 mg/dL), with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/L (160 mg/dL) in the RoActemra subcutaneous weekly group.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

There are limited data available on overdose with RoActemra. One case of accidental overdose was reported in which a patient with multiple myeloma received a single dose of 40 mg/kg administered intravenously. No adverse reactions were observed.

No serious adverse reactions were observed in healthy volunteers who received a single dose up to 28 mg/kg, although dose limiting neutropenia was observed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors; ATC code: L04AC07.

Mechanism of action

RoActemra binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis and neoplasia.

Pharmacodynamic effects

In RA clinical studies with RoActemra, rapid decreases in CRP, erythrocyte sedimentation rate (ESR) and serum amyloid A (SAA) were observed. Consistent with the effect on acute phase reactants, treatment with RoActemra was associated with reduction in platelet count within the normal range. Increases in haemoglobin levels were observed, through RoActemra decreasing the IL-6 driven effects on hepcidin production to increase iron availability. In RoActemra-treated patients, decreases in the levels of CRP to within normal ranges were seen as early as week 2, with decreases maintained while on treatment.

In GCA clinical study WA28119, similar rapid decreases in CRP and ESR were observed along with slight increases in mean corpuscular haemoglobin concentration. In healthy subjects administered RoActemra in doses from 2 to 28 mg/kg intravenously and 81 to 162 mg subcutaneously, absolute neutrophil counts decreased to their lowest 2 to 5 days following administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. RA and GCA patients demonstrate a comparable (to healthy subjects) decrease of absolute neutrophil counts following RoActemra administration (see section 4.8).

RA

Intravenous use

Clinical efficacy

The efficacy of tocilizumab 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 eight tender and six swollen joints at baseline.

In Study I, RoActemra was administered intravenously every four weeks as monotherapy. In Studies II, III and V, RoActemra was administered intravenously every four weeks in combination with MTX vs. placebo and MTX. In Study IV, RoActemra was administered intravenously every 4 weeks in

combination with other DMARDs vs. placebo and other DMARDs. The primary endpoint for each of the five studies was the proportion of patients who achieved an ACR 20 response at week 24.

Study I evaluated 673 patients who had not been treated with MTX within six months prior to randomisation and who had not discontinued previous MTX treatment as a result of clinically important toxic effects or lack of response. The majority (67%) of patients were MTX-naïve. Doses of 8 mg/kg of RoActemra were given every four weeks as monotherapy. The comparator group was weekly MTX (dose titrated from 7.5 mg to a maximum of 20 mg weekly over an eight week period).

Study II, a two year study with planned analyses at week 24, week 52 and week 104, evaluated 1196 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of RoActemra or placebo were given every four weeks as blinded therapy for 52 weeks in combination with stable MTX (10 mg to 25 mg weekly). After week 52, all patients could receive open-label treatment with RoActemra 8 mg/kg. Of the patients who completed the study who were originally randomised to placebo + MTX, 86% received open-label RoActemra 8 mg/kg in year 2. The primary endpoint at week 24 was the proportion of patients who achieved an ACR 20 response. At week 52 and week 104 the co-primary endpoints were prevention of joint damage and improvement in physical function.

Study III evaluated 623 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg RoActemra or placebo were given every four weeks, in combination with stable MTX (10 mg to 25 mg weekly).

Study IV evaluated 1,220 patients who had an inadequate response to their existing rheumatologic therapy, including one or more DMARDs. Doses of 8 mg/kg RoActemra or placebo were given every four weeks in combination with stable DMARDs.

Study V evaluated 499 patients who had an inadequate clinical response or were intolerant to one or more TNF antagonist therapies. The TNF antagonist therapy was discontinued prior to randomisation. Doses of 4 or 8 mg/kg tocilizumab or placebo were given every four weeks in combination with stable MTX (10 mg to 25 mg weekly).

Clinical response

In all studies, patients treated with RoActemra 8 mg/kg had statistically significant higher ACR 20, 50, 70 response rates at 6 months compared to control (Table 2). In study I, superiority of RoActemra 8 mg/kg was demonstrated against the active comparator MTX.

The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race, number of prior treatments or disease status. Time to onset was rapid (as early as week 2) and the magnitude of response continued to improve with duration of treatment. Continued durable responses were seen for over 3 years in the ongoing open label extension studies I-V.

In patients treated with RoActemra 8 mg/kg, significant improvements were noted on all individual components of the ACR response including: tender and swollen joint counts; patients and physician global assessment; disability index scores; pain assessment and CRP compared to patients receiving placebo plus MTX or other DMARDs in all studies.

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

In a pooled analysis of studies II, III and IV, the proportion of patients achieving an ACR 20, 50 and 70 response was significantly higher (59% vs. 50%, 37% vs. 27%, 18% vs. 11%, respectively) in the tocilizumab 8 mg/kg plus DMARD vs. the tocilizumab 4 mg/kg plus DMARD group ($p < 0.03$). Similarly the proportion of patients achieving a DAS 28 remission (DAS28 < 2.6) was significantly

higher (31% vs. 16% respectively) in patients receiving RoActemra 8 mg/kg plus DMARD than in patients receiving RoActemra 4 mg/kg plus DMARD ($p < 0.0001$).

Table 2. ACR responses in placebo-/MTX-/DMARDs-controlled studies (% 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	PBO + MTX	TCZ 8 mg/kg + MTX	PBO + MTX	TCZ 8 mg/kg + DMARD	PBO + DMARD	TCZ 8 mg/kg + MTX	PBO + MTX
	N = 286	N = 284	N = 398	N = 393	N = 205	N = 204	N = 803	N = 413	N = 170	N = 158
ACR 20										
24	70%** *	52%	56%** *	27%	59%** *	26%	61%***	24%	50%** *	10%
52			56%** *	25%						
ACR 50										
24	44%**	33%	32%** *	10%	44%** *	11%	38%***	9%	29%** *	4%
52			36%** *	10%						
ACR 70										
24	28%**	15%	13%** *	2%	22%** *	2%	21%***	3%	12%**	1%
52			20%** *	4%						

TCZ - Tocilizumab

MTX - Methotrexate

PBO - Placebo

DMARD - Disease modifying anti-rheumatic drug

** - $p < 0.01$, TCZ vs. PBO + MTX/DMARD

*** - $p < 0.0001$, TCZ vs. PBO + MTX/DMARD

Major clinical response

After 2 years of treatment with tocilizumab plus MTX, 14% of patients achieved a major clinical response (maintenance of an ACR70 response for 24 weeks or more).

Radiographic response

In Study II, in patients with an inadequate response to MTX, inhibition of structural joint damage was assessed radiographically and expressed as change in modified Sharp score and its components, the erosion score and joint space narrowing score. Inhibition of joint structural damage was shown with significantly less radiographic progression in patients receiving RoActemra compared to control (Table 3).

In the open-label extension of Study II the inhibition of progression of structural joint damage in tocilizumab plus MTX-treated patients was maintained in the second year of treatment. The mean change from baseline at week 104 in total Sharp-Genant score was significantly lower for patients randomised to RoActemra 8 mg/kg plus MTX ($p < 0.0001$) compared with patients who were randomised to placebo plus MTX.

Table 3. Radiographic mean changes over 52 weeks in Study II

	PBO + MTX (+ TCZ from week 24) N = 393	TCZ 8 mg/kg + MTX N = 398
Total Sharp-Genant score	1.13	0.29*
Erosion score	0.71	0.17*
JSN score	0.42	0.12**

PBO - Placebo

MTX - Methotrexate

TCZ - Tocilizumab

JSN - Joint space narrowing

* - $p \leq 0.0001$, TCZ vs. PBO + MTX

** - $p < 0.005$, TCZ vs. PBO + MTX

Following 1 year of treatment with tocilizumab plus MTX, 85% of patients (n=348) had no progression of structural joint damage, as defined by a change in the Total Sharp Score of zero or less, compared with 67% of placebo plus MTX-treated patients (n=290) ($p \leq 0.001$). This remained consistent following 2 years of treatment (83%; n=353). Ninety three percent (93%; n=271) of patients had no progression between week 52 and week 104.

Health-related and quality of life outcomes

RoActemra -treated patients reported an improvement in all patient-reported outcomes (Health Assessment Questionnaire Disability Index - HAQ-DI), Short Form-36 and Functional Assessment of Chronic Illness Therapy questionnaires. Statistically significant improvements in HAQ-DI scores were observed in patients treated with RoActemra compared with patients treated with DMARDs. During the open-label period of Study II, the improvement in physical function has been maintained for up to 2 years. At Week 52, the mean change in HAQ-DI was -0.58 in the RoActemra 8 mg/kg plus MTX group compared with -0.39 in the placebo + MTX group. The mean change in HAQ-DI was maintained at Week 104 in the RoActemra 8 mg/kg plus MTX group (-0.61).

Haemoglobin levels

Statistically significant improvements in haemoglobin levels were observed with RoActemra compared with DMARDs ($p < 0.0001$) at week 24. Mean haemoglobin levels increased by week 2 and remained within normal range through to week 24.

Tocilizumab versus adalimumab in monotherapy

Study VI (WA19924), a 24 week double-blinded study that compared RoActemra monotherapy with adalimumab monotherapy, evaluated 326 patients with RA who were intolerant of MTX or where continued treatment with MTX was considered inappropriate (including MTX inadequate responders). Patients in the RoActemra arm received an intravenous (IV) infusion of RoActemra (8 mg/kg) every 4 weeks (q4w) and a subcutaneous (SC) placebo injection every 2 weeks (q2w). Patients in the adalimumab arm received an adalimumab SC injection (40 mg) q2w plus an IV placebo infusion q4w.

A statistically significant superior treatment effect was seen in favour of RoActemra over adalimumab in control of disease activity from baseline to week 24 for the primary endpoint of change in DAS28 and for all secondary endpoints (Table 4).

Table 4: Efficacy Results for Study VI (WAI9924)

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

^ap value is adjusted for region and duration of RA for all endpoints and additionally baseline value for all continuous endpoints.

^b Non-responder Imputation used for missing data. Multiplicity controlled using Bonferroni-Holm Procedure

The overall clinical adverse event profile was similar between tocilizumab and adalimumab. The proportion of patients with serious adverse events was balanced between the treatment groups (RoActemra 11.7% vs. adalimumab 9.9%). The types of adverse drug reactions in the tocilizumab arm were consistent with the known safety profile of RoActemra and adverse drug reactions were reported at a similar frequency compared with Table 1. A higher incidence of infections and infestations was reported in the RoActemra arm (48% vs. 42%), with no difference in the incidence of serious infections (3.1%). Both study treatments induced the same pattern of changes in laboratory safety parameters (decreases in neutrophil and platelet counts, increases in ALT, AST and lipids), however, the magnitude of change and the frequency of marked abnormalities was higher with RoActemra compared with adalimumab. Four (2.5%) patients in the RoActemra arm and two (1.2%) patients in the adalimumab arm experienced CTC grade 3 or 4 neutrophil count decreases. Eleven (6.8%) patients in the RoActemra arm and five (3.1%) patients in the adalimumab arm experienced ALT increases of CTC grade 2 or higher. The mean LDL increase from baseline was 0.64 mmol/L (25 mg/dL) for patients in the RoActemra arm and 0.19 mmol/L (7 mg/dL) for patients in the adalimumab arm. The safety observed in the tocilizumab arm was consistent with the known safety profile of RoActemra and no new or unexpected adverse drug reactions were observed (see Table 1).

Subcutaneous use

Clinical efficacy

The efficacy of subcutaneous administered RoActemra in alleviating the signs and symptoms of RA and radiographic response, was assessed in two randomised, double-blind, controlled, multi-center studies. For study I (SC-I), patients were required to be >18 years of age with moderate to severe active RA diagnosed according to ACR criteria who had at least 4 tender and 4 swollen joints at baseline. All patients received background non-biologic DMARD(s). For study II (SC-II), patients were required to be > 18 years of age with moderate to severe active RA diagnosed according to ACR criteria who had at least 8 tender and 6 swollen joints at baseline.

Switching from 8 mg/kg intravenous once every 4 weeks to 162 mg subcutaneous once every week, will alter exposure in the patient. The extent varies with the patient's body weight (increased in light body weight patients and decreased in heavy body weight patients) but clinical outcome is consistent with that observed in intravenous treated patients.

Clinical response

Study SC-I evaluated patients with moderate to severe active RA who had an inadequate clinical response to their existing rheumatologic therapy, including one or more DMARD(s) where approximately 20% had a history of inadequate response to at least one TNF inhibitor. In SC-I, 1262 patients were randomized 1:1 to receive RoActemra subcutaneous 162 mg every week or RoActemra intravenous 8 mg/kg every four weeks in combination with non-biologic DMARD(s). The primary endpoint in the study was the difference in the proportion of patients who achieved an ACR20 response at week 24. The results from study SC-I is shown in Table 5.

Table 5. ACR responses in study SC-I (% patients) at Week 24

	SC-I ^a	
	TCZ SC 162 mg every week + DMARD N=558	TCZ IV 8 mg/kg + DMARD N=537
ACR20 Week 24	69.4%	73.4%
Weighted difference (95% CI)	-4.0 (-9.2, 1.2)	
ACR50 Week 24	47.0%	48.6%
Weighted difference (95% CI)	-1.8 (-7.5, 4.0)	
ACR70 Week 24	24.0%	27.9%
Weighted difference (95% CI)	-3.8 (-9.0, 1.3)	

TCZ = tocilizumab

a = Per Protocol Population

Patients in study SC-I had a mean Disease Activity Score (DAS28) at baseline of 6.6 and 6.7 on the subcutaneous and intravenous arms, respectively. At week 24, a significant reduction in DAS28 from baseline (mean improvement) of 3.5 was observed on both treatment arms, and a comparable proportion of patients had achieved DAS28 clinical remission (DAS28 < 2.6) on the subcutaneous (38.4%) and IV (36.9%) arms.

Radiographic response

The radiographic response of subcutaneous administered RoActemra was assessed in a double-blind, controlled, multicenter study in patients with active RA (SC-II). Study SC-II evaluated patients with moderate to severe active RA who had an inadequate clinical response to their existing rheumatologic therapy, including one or more DMARD(s) where approximately 20% had a history of inadequate response to at least one TNF inhibitor. Patients were required to be >18 years of age with active RA diagnosed according to ACR criteria who had at least 8 tender and 6 swollen joints at baseline. In SC-II, 656 patients were randomized 2:1 to RoActemra subcutaneous 162 mg every other week or placebo, in combination with non-biologic DMARD(s).

In study SC-II, inhibition of structural joint damage was assessed radiographically and expressed as a change from baseline in the van der Heijde modified mean total Sharp score (mTSS). At week 24, inhibition of structural damage was shown, with significantly less radiographic progression in patients receiving RoActemra subcutaneous compared to placebo (mean mTSS of 0.62 vs. 1.23, p=0.0149 (van Elteren). These results are consistent with those observed in patients treated with intravenous tocilizumab.

In study SC-II, at week 24 there was ACR20 of 60.9%, ACR50 of 39.8% and ACR70 of 19.7% for patients treated with RoActemra subcutaneous every other week versus placebo ACR20 of 31.5%, ACR50 of 12.3% and ACR70 of 5.0%. Patients had mean DAS28 at baseline of 6.7 on subcutaneous and 6.6 on placebo arms. At week 24, a significant reduction in DAS28 from baseline of 3.1 was observed on subcutaneous and 1.7 on placebo arm, and for DAS28 < 2.6, 32.0% was observed on subcutaneous and 4.0% on placebo arm.

Health-related and quality of life outcomes

In study SC-I, the mean decrease in HAQ-DI from baseline to week 24 was 0.6 on both the subcutaneous and intravenous arms. The proportion of patients achieving a clinically relevant improvement in HAQ-DI at week 24 (change from baseline of ≥ 0.3 units) was also comparable on the subcutaneous (65.2%) versus intravenous (67.4%) arms, with a weighted difference in proportions of -2.3% (95% CI - 8.1, 3.4). For SF-36, the mean change from baseline at week 24 in the mental component score was 6.22 for the subcutaneous arm and 6.54 for the intravenous arm, and for the physical component score was also similar with 9.49 for the subcutaneous arm and 9.65 for the intravenous arm.

In study SC-II, mean decrease in HAQ-DI from baseline to week 24 was significantly greater for patients treated with tocilizumab subcutaneous every other week (0.4) versus placebo (0.3). Proportion of patients achieving a clinically relevant improvement in HAQ-DI at week 24 (change from baseline of ≥ 0.3 units) was higher for tocilizumab subcutaneous every other week (58%) versus placebo (46.8%). SF-36 (mean change in mental and physical component scores) was significantly greater with tocilizumab subcutaneous group (6.5 and 5.3) versus placebo (3.8 and 2.9).

GCA

Subcutaneous Use

Clinical efficacy

Study WA28119 was a randomized, multi-center, double-blind placebo-controlled Phase III superiority study conducted to assess the efficacy and safety of RoActemra in patients with GCA.

Two hundred and fifty one (251) patients with new-onset or relapsing GCA were enrolled and assigned to one of four treatment arms. The study consisted of a 52-week blinded period (Part 1), followed by a 104-week open-label extension (Part 2). The purpose of Part 2 was to describe the long-term safety and maintenance of efficacy after 52 weeks of RoActemra therapy, to explore the rate of relapse and the requirement for RoActemra therapy beyond 52 weeks, and to gain insight into the potential long-term steroid-sparing effect of RoActemra.

Two subcutaneous doses of RoActemra (162 mg every week and 162 mg every other week) were compared to two different placebo control groups randomised 2:1:1:1.

All patients received background glucocorticoid (prednisone) therapy. Each of the RoActemra-treated groups and one of the placebo-treated groups followed a pre-specified prednisone-taper regimen over 26 weeks, while the second placebo-treated group followed a pre-specified prednisone-taper regimen over 52 weeks, designed to be more in keeping with standard practice.

The duration of glucocorticoid therapy during screening and before RoActemra (or placebo) was initiated, was similar in all 4 treatment groups (see Table 6).

Table 6. Duration of Corticosteroid Therapy During Screening in Study WA28119

	Placebo + 26 weeks prednisone taper N=50	Placebo + 52 weeks prednisone taper N=51	RoActemra 162mg SC weekly + 26 weeks prednisone taper N=100	RoActemra 162 mg SC every other weekly + 26 weeks prednisone taper N=49
Duration (days)				
Mean (SD)	35.7 (11.5)	36.3 (12.5)	35.6 (13.2)	37.4 (14.4)
Median	42.0	41.0	41.0	42.0
Min - Max	6 - 63	12 - 82	1 - 87	9 - 87

The primary efficacy endpoint assessed by the proportion of patients achieving steroid free sustained remission at week 52 on RoActemra plus 26 weeks prednisone taper compared with placebo plus 26 weeks prednisone taper, was met (Table 7).

The key secondary efficacy endpoint also based on the proportion of patients achieving sustained remission at week 52, comparing tocilizumab plus 26 weeks prednisone taper with placebo plus 52 weeks prednisone taper, was also met (Table 7).

A statistically significant superior treatment effect was seen in favour of RoActemra over placebo in achieving steroid-free sustained remission at week 52 on RoActemra plus 26 weeks prednisone taper compared with placebo plus 26 weeks prednisone taper and with placebo plus 52 weeks prednisone taper.

The percentage of patients achieving sustained remission at week 52, are shown in the Table 7.

Secondary Endpoints

The assessment of the time to first GCA flare showed a significantly lower risk of flare for the RoActemra subcutaneous weekly group compared to placebo plus 26 weeks prednisone and placebo plus 52 weeks prednisone taper groups and for the RoActemra subcutaneous every other weekly group compared to placebo plus 26 weeks prednisone (when compared at a 0.01 significance level). RoActemra subcutaneous weekly dose also showed a clinically meaningful decrease in the risk for flare compared to placebo plus 26 weeks prednisone in patients who entered the trial with relapsing GCA as well as those with new-onset disease (Table 7).

Cumulative glucocorticoid dose

The cumulative prednisone dose at week 52 was significantly lower in the two RoActemra dose groups compared to the two placebo groups (Table 6). In a separate analysis of the patients who received escape prednisone to treat GCA flare during the first 52 weeks, the cumulative prednisone dose varied greatly. The median doses for escape patients in the RoActemra weekly and every other weekly groups were 3129.75 mg and 3847 mg, respectively. Both considerably lower than in the placebo plus 26 weeks and the placebo plus 52 weeks prednisone taper groups, 4023.5 mg and 5389.5 mg respectively.

Table 7. Efficacy results from Study WA28119

	Placebo + 26 weeks prednisone taper N=50	Placebo + 52 weeks prednisone taper N=51	RoActemra 162mg SC weekly + 26 weeks prednisone taper N=100	RoActemra 162 mg SC every other weekly + 26 weeks prednisone taper N=49
Primary Endpoint				
****Sustained remission (Tocilizumab groups vs Placebo+26)				
Responders at Week 52, n (%)	7 (14%)	9 (17.6%)	56 (56%)	26 (53.1%)
Unadjusted difference in proportions (99.5% CI)	N/A	N/A	42%* (18.00, 66.00)	39.06%* (12.46, 65.66)
Key Secondary Endpoint				
Sustained remission (Tocilizumab groups vs Placebo+52)				
Responders at Week 52, n (%)	7 (14%)	9 (17.6%)	56 (56%)	26 (53.1%)
Unadjusted difference in proportions (99.5% CI)	N/A	N/A	38.35%* (17.89, 58.81)	35.41%** (10.41, 60.41)
Other Secondary Endpoints				
Time to first GCA flare ¹ (Tocilizumab groups vs Placebo+26)	N/A	N/A	0.23* (0.11, 0.46)	0.28** (0.12, 0.66)
HR (99% CI)	N/A	N/A	0.39**	0.48
Time to first GCA flare ¹ (Tocilizumab groups vs Placebo+52)			(0.18, 0.82)	(0.20, 1.16)
HR (99% CI)	N/A	N/A	0.23***	0.42
Time to first GCA flare ¹ (Relapsing patients; Tocilizumab groups vs Placebo +26) HR (99% CI)	N/A	N/A	(0.09, 0.61)	(0.14, 1.28)
Time to first GCA flare ¹ (Relapsing patients; Tocilizumab groups vs Placebo + 52) HR (99% CI)	N/A	N/A	0.36 (0.13, 1.00)	0.67 (0.21, 2.10)
Time to first GCA flare ¹ (New-onset patients; Tocilizumab groups vs Placebo + 26) HR (99% CI)	N/A	N/A	0.25*** (0.09, 0.70)	0.20*** (0.05, 0.76)
Time to first GCA flare ¹ (New-onset patients; Tocilizumab groups vs Placebo + 52) HR (99% CI)	N/A	N/A	0.44 (0.14, 1.32)	0.35 (0.09, 1.42)
<i>Cumulative glucocorticoid dose (mg)</i>				
median at Week 52 (Tocilizumab groups vs Placebo+26 ²)	3296.00	N/A	1862.00*	1862.00*
median at Week 52 (Tocilizumab groups vs Placebo +52 ²)	N/A	3817.50	1862.00*	1862.00*
Exploratory Endpoints				
Annualized relapse rate, Week 52 [§]				
Mean (SD)	1.74 (2.18)	1.30 (1.84)	0.41 (0.78)	0.67 (1.10)

* p<0.0001

** p<0.005 (threshold for significance for primary and key secondary tests of superiority)

***Descriptive p value ≤0.005

****Flare: recurrence of GCA signs or symptoms and/or ESR ≥30 mm/h – Increase in the prednisone dose required

Remission: absence of flare and normalization of the CRP

Sustained remission: remission from week 12 to week 52 –Patients must adhere to the protocol-defined prednisone taper

¹ analysis of the time (in days) between clinical remission and first disease flare

² p-values are determined using a Van Elteren analysis for non-parametric data

[§] statistical analyses has not been performed

N/A= Not applicable

HR = Hazard Ratio

CI = Confidence Interval

Quality of Life Outcomes

In study WA28119, the SF-36 results were separated into the physical and mental component summary scores (PCS and MCS, respectively). The PCS mean change from baseline to week 52 was higher (showing more improvement) in the RoActemra weekly and every other weekly dose groups [4.10, 2.76, respectively] than in the two placebo groups [placebo plus 26 weeks; -0.28, placebo plus 52 weeks; -1.49], although only the comparison between RoActemra weekly plus 26 weeks prednisone taper group and placebo plus 52 weeks prednisone taper group (5.59, 99% CI: 8.6, 10.32) showed a statistically significant difference ($p=0.0024$). For MCS, the mean change from baseline to week 52 for both RoActemra weekly and every other weekly dose groups [7.28, 6.12, respectively] were higher than the placebo plus 52 weeks prednisone taper group [2.84] (although the differences were not statistically significant [weekly $p=0.0252$ for weekly, $p=0.1468$ for every other weekly]) and similar to the placebo plus 26 weeks prednisone taper group [6.67].

The Patient's Global Assessment of disease activity was assessed on a 0-100mm Visual Analogue Scale (VAS). The mean change in Patient's global VAS from baseline at week 52 was lower (showing greater improvement) in the RoActemra weekly and every other weekly dose groups [-19.0, -25.3, respectively] than in both placebo groups [placebo plus 26 weeks -3.4, placebo plus 52 weeks -7.2], although only the RoActemra every other weekly plus 26 weeks prednisone taper group showed a statistically significant difference compared to placebo [placebo plus 26 weeks taper $p=0.0059$, and placebo plus 52 weeks taper $p=0.0081$].

FACIT-Fatigue change from baseline to week 52 scores were calculated for all groups. The mean [SD] change scores were as follows: RoActemra weekly plus 26 weeks 5.61 [10.115], RoActemra every other weekly plus 26 weeks 1.81 [8.836], placebo plus 26 weeks 0.26 [10.702], and placebo plus 52 weeks -1.63 [6.753].

Change in EQ5D scores from baseline to week 52 were RoActemra weekly plus 26 weeks 0.10 [0.198], RoActemra every other weekly plus 26 weeks 0.05 [0.215], placebo plus 26 weeks 0.07 [0.293], and placebo plus 52 weeks -0.02 [0.159].

Higher scores signal improvement in both FACIT-Fatigue and EQ5D.

The European Medicines Agency has deferred the obligation to submit the results of studies with RoActemra in one or more subsets of the paediatric population in the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, ankylosing spondylarthritis, psoriatic arthritis and juvenile idiopathic arthritis). See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

The pharmacokinetics of RoActemra is characterized by nonlinear elimination which is a combination of linear clearance and Michaelis-Menten elimination. The nonlinear part of RoActemra elimination leads to an increase in exposure that is more than dose-proportional. The pharmacokinetic parameters of RoActemra do not change with time. Due to the dependence of total clearance on RoActemra serum concentrations, the half-life of RoActemra is also concentration-dependent and varies depending on the serum concentration level. Population pharmacokinetic analyses in any patient population tested so far indicate no relationship between apparent clearance and the presence of anti-drug antibodies.

RA

Intravenous use

The pharmacokinetics of RoActemra were determined using a population pharmacokinetic analysis on a database composed of 3552 RA patients treated with a one-hour infusion of 4 or 8 mg/kg RoActemra every 4 weeks for 24 weeks or with 162 mg tocilizumab given subcutaneously either once a week or every other week for 24 weeks.

The following parameters (predicted mean \pm SD) were estimated for a dose of 8 mg/kg RoActemra given every 4 weeks: steady-state area under curve (AUC) = 38000 ± 13000 h \cdot μ g/mL, trough

concentration (C_{min}) = 15.9 ± 13.1 $\mu\text{g/mL}$ and maximum concentration (C_{max}) = 182 ± 50.4 $\mu\text{g/mL}$, and the accumulation ratios for AUC and C_{max} were small, 1.32 and 1.09, respectively. The accumulation ratio was higher for C_{min} (2.49), which was expected based on the non-linear clearance contribution at lower concentrations. Steady-state was reached following the first administration for C_{max} and after 8 and 20 weeks for AUC and C_{min} , respectively. RoActemra AUC, C_{min} and C_{max} increased with increase of body weight. At body weight ≥ 100 kg, the predicted mean (\pm SD) steady-state AUC, C_{min} and C_{max} of RoActemra were 50000 ± 16800 $\mu\text{g}\cdot\text{h/mL}$, 24.4 ± 17.5 $\mu\text{g/mL}$, and 226 ± 50.3 $\mu\text{g/mL}$, respectively, which are higher than mean exposure values for the patient population (i.e. all body weights) reported above. The dose-response curve for tocilizumab flattens at higher exposure, resulting in smaller efficacy gains for each incremental increase in RoActemra concentration such that clinically meaningful increases in efficacy were not demonstrated in patients treated with > 800 mg of RoActemra. Therefore, RoActemra doses exceeding 800 mg per infusion are not recommended (see section 4.2).

Distribution

In RA patients the central volume of distribution was 3.72, the peripheral volume of distribution was 3.35 resulting in a volume of distribution at steady state of 7.07.

Elimination

Following intravenous administration, RoActemra undergoes biphasic elimination from the circulation. The total clearance of RoActemra was concentration-dependent and is the sum of the linear and non-linear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 9.5 ml/h. The concentration-dependent non-linear clearance plays a major role at low RoActemra concentrations. Once the non-linear clearance pathway is saturated, at higher RoActemra concentrations, clearance is mainly determined by the linear clearance.

The $t_{1/2}$ of RoActemra was concentration-dependent. At steady-state following a dose of 8 mg/kg every 4 weeks, the effective $t_{1/2}$ decreased with decreasing concentrations within a dosing interval from 18 days to 6 days.

Linearity

Pharmacokinetic parameters of RoActemra did not change with time. A more than dose-proportional increase in the AUC and C_{min} was observed for doses of 4 and 8 mg/kg every 4 weeks. C_{max} increased dose-proportionally. At steady-state, predicted AUC and C_{min} were 3.2 and 30 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively.

Subcutaneous use

The pharmacokinetics of RoActemra were determined using a population pharmacokinetic analysis on a database composed of 3552 RA patients treated with 162 mg subcutaneous every week, 162 mg subcutaneous every other week, and or 4 or 8 mg/kg intravenous every 4 weeks for 24 weeks.

The pharmacokinetic parameters of RoActemra did not change with time. For the 162 mg every week dose, the predicted mean (\pm SD) steady-state AUC_{1week}, C_{min} and C_{max} of RoActemra were 7970 ± 3432 $\mu\text{g}\cdot\text{h/mL}$, 43.0 ± 19.8 $\mu\text{g/mL}$, and 49.8 ± 21.0 $\mu\text{g/mL}$, respectively. The accumulation ratios for AUC, C_{min} , and C_{max} were 6.32, 6.30, and 5.27, respectively. Steady state was reached after 12 weeks for AUC, C_{min} , and C_{max} .

For the 162 every other week dose, the predicted mean (\pm SD) steady-state AUC_{2week}, C_{min} , and C_{max} of RoActemra were 3430 ± 2660 $\mu\text{g}\cdot\text{h/mL}$, 5.7 ± 6.8 $\mu\text{g/mL}$, and 13.2 ± 8.8 $\mu\text{g/mL}$, respectively. The accumulation ratios for AUC, C_{min} , and C_{max} were 2.67, 6.02, and 2.12, respectively. Steady state was reached after 12 weeks for AUC and C_{min} , and after 10 weeks for C_{max} .

Absorption

Following subcutaneous dosing in RA patients, the time to peak serum RoActemra concentrations t_{max} was 2.8 days. The bioavailability for the subcutaneous formulation was 79%.

Elimination

For subcutaneous administration, the concentration-dependent apparent $t_{1/2}$ is up to 12 days for 162 mg every week and 5 days for 162 mg every other week in patients with RA at steady-state.

GCA

Subcutaneous use

The PK of RoActemra in GCA patients were determined using a population PK model from an analysis dataset composed of 149 GCA patients treated with 162 mg subcutaneous every week or 162 mg subcutaneous every other week. The developed model had the same structure as the population PK model developed earlier based on data from RA patients (see Table 8).

Table 8. Predicted mean \pm SD PK parameters at steady-state after subcutaneous dosing in GCA

Tocilizumab PK Parameter	Subcutaneous	
	162 mg every other weekly	162 mg weekly
C_{\max} ($\mu\text{g/mL}$)	19.3 \pm 12.8	73 \pm 30.4
C_{trough} ($\mu\text{g/mL}$)	11.1 \pm 10.3	68.1 \pm 29.5
C_{mean} ($\mu\text{g/mL}$)	16.2 \pm 11.8	71.3 \pm 30.1
Accumulation C_{\max}	2.18	8.88
Accumulation C_{trough}	5.61	9.59
Accumulation C_{mean} or AUC_{τ}	2.81	10.91

The steady-state profile following the RoActemra weekly dose was almost flat, with very little fluctuations between trough and peak values, while there were substantial fluctuations for the RoActemra every other weekly dose. Approximately 90% of the steady-state (AUC_{τ}) was reached by week 14 in the every other weekly and week 17 in the weekly dose groups.

Based on the current characterization of PK, RoActemra trough concentration at steady state are 50% higher in this population relative to average concentrations in a large dataset from the RA population. These differences occur due to unknown reasons. PK differences are not accompanied by marked differences in PD parameters and so the clinical relevance is unknown.

In GCA patients, higher exposure was observed in patients with lower body weight. For the 162 mg every week dosing regimen, the steady-state C_{avg} was 51% higher in patients with body weight less than 60 kg compared to patients weighing between 60 to 100 kg. For the 162 mg every other week regimen, the steady-state C_{avg} was 129% higher in patients with body weight less than 60 kg compared to patients weighing between 60 to 100 kg. There is limited data for patients above 100 kg ($n=7$).

Absorption

Following subcutaneous dosing in GCA patients, the absorption $t_{1/2}$ was around 4 days. The bioavailability for the SC formulation was 0.8. The median values of T_{\max} were 3 days after the RoActemra weekly dose and 4.5 days after the tocilizumab every other week dose.

Distribution

In GCA patients, the central volume of distribution was 4.09 L, the peripheral volume of distribution was 3.37 L, resulting in a volume of distribution at steady state of 7.46 L.

Elimination

The total clearance of RoActemra was concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 6.7 mL/h in GCA patients,

In GCA patients, at steady state, the effective $t_{1/2}$ of RoActemra varied between 18.3 and 18.9 days for 162 mg weekly regimen, and between 4.2 and 7.9 days for 162 mg every other weekly regimen. At high serum concentrations, when total clearance of RoActemra is dominated by linear clearance, an effective $t_{1/2}$ of approximately 32 days was derived from the population parameter estimates.

Special populations

Renal impairment: No formal study of the effect of renal impairment on the pharmacokinetics of RoActemra has been conducted. Most of the patients in the RA and GCA studies population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (estimated creatinine clearance based on Cockcroft-Gault formula) did not impact the pharmacokinetics of RoActemra.

Approximately one-third of the patients in the GCA study had moderate renal impairment at baseline (estimated creatinine clearance of 30-59 mL/min). No impact on RoActemra exposure was noted in these patients.

No dose adjustment is required in patients with mild or moderate renal impairment.

Hepatic impairment: No formal study of the effect of hepatic impairment on the pharmacokinetics of RoActemra has been conducted.

Age, gender and ethnicity: Population pharmacokinetic analyses in RA and GCA patients, showed that age, gender and ethnic origin did not affect the pharmacokinetics of RoActemra.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

Carcinogenicity studies were not performed because IgG1 monoclonal antibodies are not deemed to have intrinsic carcinogenic potential.

Available non-clinical data demonstrated the effect of IL-6 on malignant progression and apoptosis resistance to various cancer types. This data does not suggest a relevant risk for cancer initiation and progression under RoActemra treatment. Additionally, proliferative lesions were not observed in a 6-month chronic toxicity study in cynomolgus monkeys or in IL-6 deficient mice.

Available non-clinical data do not suggest an effect on fertility under tocilizumab treatment. Effects on endocrine active and reproductive system organs were not observed in a chronic cynomolgus monkey toxicity study and reproductive performance was not affected in IL-6 deficient mice. RoActemra administered to cynomolgus monkeys during early gestation, was observed to have no direct or indirect harmful effect on pregnancy or embryonal-foetal development. However, a slight increase in abortion/embryonal-foetal death was observed with high systemic exposure ($> 100 \times$ human exposure) in the 50 mg/kg/day high-dose group compared to placebo and other low-dose groups. Although IL-6 does not seem to be a critical cytokine for foetal growth or the immunological control of the maternal/foetal interface, a relation of this finding to RoActemra cannot be excluded.

Treatment with a murine analogue did not exert toxicity in juvenile mice. In particular, there was no impairment of skeletal growth, immune function and sexual maturation.

The non-clinical safety profile of RoActemra in the cynomolgus monkey does not suggest a difference between intravenous and subcutaneous routes of administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine
L-Histidine monohydrochloride monohydrate
L-Arginine
L-Arginine hydrochloride
L-Methionine
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

24 months.

Once removed from the refrigerator, RoActemra must be administered within 8 hours and should not be kept above 30°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C). Do not freeze.

Keep the pre-filled syringes in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

0.9 ml solution in a pre-filled syringe (type I glass) with a staked-in needle. The syringe is closed by a rigid needle shield (elastomer seal with a polypropylene shell) and a plunger stopper (butyl rubber with a fluororesin coating).

Pack sizes of 4 pre-filled syringes **and multipacks containing 12 (3 packs of 4) pre-filled syringes.**
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

RoActemra is supplied in a single use pre-filled syringe fitted into a needle safety device. After removing the pre-filled syringe from the refrigerator the pre-filled syringe should be allowed to reach room temperature (18°C to 28°C) by waiting for 25 to 30 minutes, before injecting RoActemra. The syringe should not be shaken. After removing the cap the injection must be started within 5 minutes, to prevent the medicine from drying out and blocking the needle. If the pre-filled syringe is not used within 5 minutes of removing the cap, you must dispose of it in a puncture resistant container and use a new pre-filled syringe.

If following insertion of the needle you cannot depress the plunger, you must dispose of the pre-filled syringe in a puncture resistant container and use a new pre-filled syringe.

Do not use if the medicine is cloudy or contains particles, is any colour besides colourless to slightly yellowish, or any part of the pre-filled syringe appears to be damaged.

Comprehensive instructions for the administration of RoActemra in a pre-filled syringe are given in the package leaflet.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

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EU/1/08/492/008

9. DATE OF FIRST AUTHORISATION/DATE OF LATEST RENEWAL

16 January 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu/>.

ANNEX II

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND
MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer of the biological active substance

Chugai Pharma Manufacturing Co., Ltd.
16-3 Kiyohara Kogyodanchi
Utsunomiya City
Tochigi, 321-3231
Japan

Genentech Inc.
One Antibody Way
Oceanside
CA 92056
USA

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
D-79639 Grenzach-Wyhlen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING
AUTHORISATION**

- Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall provide an educational pack covering the therapeutic indications RA, sJIA, pJIA and GCA, targeting all physicians who are expected to prescribe/use RoActemra containing the following:

- Physician Information Pack
- Nurse Information Pack
- Patient Information Pack

The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority prior to distribution of the educational material.

The Physician Information pack should contain the following key elements:

- The Summary of Product Characteristics
- Dose calculation (RA, sJIA and pJIA patients), preparation of infusion and infusion rate
- Risk of serious infections
 - The product must not be given to patients with active or suspected infection
 - The product may lessen signs and symptoms of acute infection delaying the diagnosis
- Serious injection/infusion reaction and their management
- Serious hypersensitivity reactions and their management
- Risk of gastrointestinal perforations especially in patients with history of diverticulitis or intestinal ulcerations
- Reporting of serious adverse drug reactions
- The Patient Information Packs (to be given to patients by healthcare professionals)
- Diagnosis of Macrophage Activation Syndrome in sJIA patients
- Recommendations for dose interruptions in sJIA and pJIA patients

The Nurse Information Pack should contain the following key elements:

- Prevention of medical errors and injection/infusion reactions
 - Preparation of injection/infusion
 - Infusion rate
- Monitoring of the patient for injection/infusion reactions
- Reporting of serious adverse reactions

The Patient Information Pack should contain the following key elements:

- Package leaflet (with instructions for use for SC)
 - Patient alert card
- to address the risk of getting infections which can become serious if not treated. In addition, some previous infections may reappear.
 - to address the risk that patients using RoActemra may develop complications of diverticulitis which can become serious if not treated.
 - to address the risk of allergic reactions.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON****1. NAME OF THE MEDICINAL PRODUCT**

RoActemra 20 mg/ml concentrate for solution for infusion
Tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 80 mg tocilizumab.

3. LIST OF EXCIPIENTS

Polysorbate 80, sucrose, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate and water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
80 mg/4 ml
1 vial of 4 ml
4 vials of 4 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous infusion after dilution
The diluted product should be used immediately
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/001
EU/1/08/492/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON****1. NAME OF THE MEDICINAL PRODUCT**

RoActemra 20 mg/ml concentrate for solution for infusion
Tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 200 mg tocilizumab.

3. LIST OF EXCIPIENTS

Polysorbate 80, sucrose, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate and water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
200 mg/10 ml
1 vial of 10 ml
4 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous infusion after dilution
The diluted product should be used immediately
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the vial in the outer carton, in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/003
EU/1/08/492/004

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON****1. NAME OF THE MEDICINAL PRODUCT**

RoActemra 20 mg/ml concentrate for solution for infusion
Tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 400 mg tocilizumab.

3. LIST OF EXCIPIENTS

Polysorbate 80, sucrose, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate and water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
400 mg/20 ml
1 vial of 20 ml
4 vials of 20 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous infusion after dilution
The diluted product should be used immediately
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the vial in the outer carton, in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/005
EU/1/08/492/006

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**PRE-FILLED SYRINGE CARTON****1. NAME OF THE MEDICINAL PRODUCT**

RoActemra 162 mg solution for injection in pre-filled syringe

Tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe contains 162 mg tocilizumab

3. LIST OF EXCIPIENTS

L-Histidine, L-Histidine monohydrochloride monohydrate, L-Arginine, L-Arginine hydrochloride, L-Methionine, Polysorbate 80, Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

4 pre-filled syringes

162 mg/0.9 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Allow the syringe to sit at room temperature outside the box for 25 to 30 minutes before use

8. EXPIRY DATE

EXP

Once removed from the refrigerator, RoActemra must be administered within 8 hours and should not be kept above 30 °C

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C–8°C)

Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/007

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

roactemra 162 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**PRE-FILLED SYRINGE CARTON (WITH BLUE BOX) - Multipack****1. NAME OF THE MEDICINAL PRODUCT**

RoActemra 162 mg solution for injection in pre-filled syringe

Tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe contains 162 mg tocilizumab

3. LIST OF EXCIPIENTS

L-Histidine, L-Histidine monohydrochloride monohydrate, L-Arginine, L-Arginine hydrochloride, L-Methionine, Polysorbate 80, Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

Multipack: 12 (3 packs of 4) pre-filled syringes.

162 mg/0.9 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Allow the syringe to sit at room temperature outside the box for 25 to 30 minutes before use

8. EXPIRY DATE

EXP

Once removed from the refrigerator, RoActemra must be administered within 8 hours and should not be kept above 30 °C

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C–8°C)

Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/008

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

roactemra 162 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**PRE-FILLED SYRINGE CARTON (WITHOUT BLUE BOX) - Multipack****1. NAME OF THE MEDICINAL PRODUCT**

RoActemra 162 mg solution for injection in pre-filled syringe

Tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe contains 162 mg tocilizumab

3. LIST OF EXCIPIENTS

L-Histidine, L-Histidine monohydrochloride monohydrate, L-Arginine, L-Arginine hydrochloride, L-Methionine, Polysorbate 80, Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

4 pre-filled syringes. Component of a multipack, can't be sold separately.

162 mg/0.9 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Allow the syringe to sit at room temperature outside the box for 25 to 30 minutes before use

8. EXPIRY DATE

EXP

Once removed from the refrigerator, RoActemra must be administered within 8 hours and should not be kept above 30 °C

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C–8°C)

Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/008

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

roactemra 162 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**VIAL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

RoActemra 20 mg/ml sterile concentrate
Tocilizumab
IV

2. METHOD OF ADMINISTRATION

IV infusion

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

80 mg/4 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**VIAL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

RoActemra 20 mg/ml sterile concentrate
Tocilizumab
IV

2. METHOD OF ADMINISTRATION

IV infusion

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg/10 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**VIAL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

RoActemra 20 mg/ml sterile concentrate
Tocilizumab
IV

2. METHOD OF ADMINISTRATION

IV infusion

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

400 mg/20 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED SYRINGE LABEL
--

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

RoActemra 162 mg injection
Tocilizumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

162 mg/0.9 ml

6. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

RoActemra 20 mg/ml concentrate for solution for infusion Tocilizumab

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

In addition to this leaflet, you will be given a **Patient Alert Card**, which contains important safety information that you need to be aware of before and during treatment with RoActemra.

What is in this leaflet:

1. What RoActemra is and what it is used for
2. What you need to know before you are given RoActemra
3. How RoActemra is given
4. Possible side effects
5. How to store RoActemra
6. Contents of the pack and other information

1. What RoActemra is and what it is used for

RoActemra contains the active substance tocilizumab, which is a protein made from specific immune cells (monoclonal antibody), that blocks the action of a specific protein (cytokine) called interleukin-6. This protein is involved in inflammatory processes of the body, and blocking it can reduce the inflammation in your body. RoActemra helps to reduce symptoms such as pain and swelling in your joints and can also improve your performance of daily tasks. RoActemra has been shown to slow the damage to the cartilage and bone of the joints caused by the disease and to improve your ability to do normal daily activities.

- **RoActemra is used to treat adults** with moderate to severe active rheumatoid arthritis (RA), an autoimmune disease, if previous therapies did not work well enough. RoActemra is usually given in combination with methotrexate. However, RoActemra can be given alone if your doctor determines that methotrexate is inappropriate.
- RoActemra can also be used to treat adults who have not had previous methotrexate treatment if they have severe, active and progressive rheumatoid arthritis.
- **RoActemra is used to treat children with sJIA.** RoActemra is used for children aged 2 years and over who have *active systemic juvenile idiopathic arthritis (sJIA)*, an inflammatory disease that causes pain and swelling in one or more joints as well as fever and rash. RoActemra is used to improve the symptoms of sJIA and can be given in combination with methotrexate or alone.
- **RoActemra is used to treat children with pJIA.** RoActemra is used for children aged 2 years and over with active *polyarticular juvenile idiopathic arthritis (pJIA)*, an inflammatory disease that causes pain and swelling in one or more joints. RoActemra is used to improve the symptoms of pJIA and can be given in combination with methotrexate or alone.

2. What you need to know before you are given RoActemra

You are not to be given RoActemra

- if you are **allergic** to tocilizumab or any of the other ingredients of this medicine (listed in Section 6).
- if you have an active, severe infection.

If any of these applies to you, tell the doctor or nurse giving you the infusion.

Warnings and precautions

Talk to your doctor or nurse before you are given RoActemra.

- If you experience **allergic reactions** such as chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips or skin rash during or after the infusion, then **tell your doctor immediately**.
- If you have any kind of **infection**, short- or long-term, or if you often get infections. **Tell your doctor immediately** if you feel unwell. RoActemra can reduce your body's ability to respond to infections and may make an existing infection worse or increase the chance of getting a new infection.
- If you have had **tuberculosis**, tell your doctor. Your doctor will check for signs and symptoms of tuberculosis before starting RoActemra. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy tell your doctor immediately.
- If you have had **intestinal ulcers** or **diverticulitis**, tell your doctor. Symptoms would include abdominal pain and unexplained changes in bowel habits with a fever.
- If you have **liver disease**, tell your doctor. Before you use RoActemra, your doctor may do a blood test to measure your liver function.
- **If any patient has recently been vaccinated** (either adult or child), or is planning a vaccination, tell your doctor. All patients, especially children, should be up-to-date with all their vaccinations before they start treatment with RoActemra. Certain types of vaccines should not be used while receiving RoActemra.
- If you have **cancer**, tell your doctor. Your doctor will have to decide if you can still be given RoActemra.
- If you have **cardiovascular risk factors** such as raised blood pressure and raised cholesterol levels, tell your doctor. These factors need to be monitored while receiving RoActemra.
- If you have moderate to severe **kidney function problems**, your doctor will monitor you.
- If you have **persistent headaches**.

Your doctor will perform blood tests before you are given RoActemra, and during your treatment, to determine if you have a low white blood cell count, low platelet count or high liver enzymes.

Children and adolescents

RoActemra is not recommended for use in children under 2 years of age.

If a child has a history of **macrophage activation syndrome**, (activation and uncontrolled proliferation of specific blood cells), tell your doctor. Your doctor will have to decide if they can still be given RoActemra.

Other medicines and RoActemra

Tell your doctor if you are taking any other medicines (or your child is, if they are the patient), or have recently taken any. This includes medicines obtained without a prescription. RoActemra can affect the way some medicines work, and the dose of these may require adjustment. If you are using medicines containing any of the following active substances, **tell your doctor**:

- methylprednisolone, dexamethasone, used to reduce inflammation
- atorvastatin, used to reduce **cholesterol levels**
- calcium channel blockers (e.g. amlodipine), used to treat **raised blood pressure**
- theophylline, used to treat **asthma**
- warfarin or phenprocoumon, used as a **blood thinning agents**
- phenytoin, used to treat **convulsions**
- ciclosporin, used to **suppress your immune system** during organ transplants
- benzodiazepines (e.g. temazepam), used to **relieve anxiety**.

Due to lack of clinical experience, RoActemra is not recommended for use with other biological medicines for the treatment of RA, sJIA or pJIA.

Pregnancy, breast-feeding and fertility

RoActemra is not to be used in pregnancy unless clearly necessary. Talk to your doctor if you are pregnant, may be pregnant, or intend to become pregnant.

Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

Stop breast-feeding if you are to be given RoActemra, and talk to your doctor. Leave a gap of at least 3 months after your last treatment before you start breast-feeding. It is not known whether RoActemra is passed into breast milk.

The data available so far does not suggest any effect on fertility from this treatment.

Driving and using machines

This medicine can cause dizziness. If you feel dizzy, do not drive or use machines.

RoActemra contains sodium

This medicine contains 26.55 mg sodium per maximum dose of 1200 mg. Take this into account if you are on a low-sodium diet. However, doses below 1025 mg of this medicine contain less than 23 mg sodium, so they are virtually sodium free.

3. How RoActemra is given

This medicine is subject to restricted medical prescription by your doctor.

RoActemra will be given to **you as a drip into a vein, by a doctor or a nurse**. They will dilute the solution, set up the intravenous infusion and monitor you during and after the treatment.

Adult patients with RA

The usual dose of RoActemra is 8 mg per kg of body weight. Depending on your response, your doctor may decrease your dose to 4 mg/kg then increase back to 8 mg/kg when appropriate.

Adults will be given RoActemra once every 4 weeks through a drip in the vein (intravenous infusion) over one hour.

Children with sJIA (aged 2 and over)

The usual dose of RoActemra depends on your weight.

- If you weigh less than 30 kg: the dose is **12 mg for every kilogram of body weight**
- If you weigh 30 kg or more, the dose is **8 mg for every kilogram of body weight**

The dose is calculated based on your body weight at each administration.

Children with sJIA will be given RoActemra once every 2 weeks through a drip in the vein (intravenous infusion) over one hour.

Children with pJIA (aged 2 and over)

The usual dose of RoActemra depends on your weight.

- If you weigh less than 30 kg: the dose is **10mg for every kilogram of body weight**
- If you weigh 30 kg or more: the dose is **8 mg for every kilogram of body weight**

The dose is calculated based on your body weight at each administration.

Children with pJIA will be given RoActemra once every 4 weeks through a drip in the vein (intravenous infusion) over one hour.

If you are given more RoActemra than you should

Since RoActemra is given by a doctor or nurse, it is unlikely that you will be given too much. However, if you are worried, talk to your doctor.

If you miss a dose of RoActemra

Since RoActemra is given by a doctor or nurse, it is unlikely that you will miss a dose. However, if you are worried, talk to your doctor or nurse.

If you stop being given RoActemra

You should not stop using RoActemra without discussing with your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, RoActemra can cause side effects, although not everybody gets them. Side effects could occur at least up to 3 months after your last dose of RoActemra.

Possible serious side effects: tell a doctor straight away.

These are common: they may affect up to 1 in every 10 users

Signs of serious infections

- fever and chills
- mouth or skin blisters
- stomach ache

If you notice any of these, tell your doctor **as soon as possible**.

Very common side effects:

These may affect more than 1 in every 10 users

- upper respiratory tract infections with typical symptoms such as cough, blocked nose, runny nose, sore throat and headache
- high blood fat (cholesterol) levels.

Common side effects:

These may affect up to 1 in every 10 users

- lung infection (pneumonia)
- shingles (herpes zoster)
- cold sores (oral herpes simplex), blisters
- skin infection (cellulitis) sometimes with fever and chills
- rash and itching, hives
- allergic (hypersensitivity) reactions
- eye infection (conjunctivitis)
- headache, dizziness, high blood pressure
- mouth ulcers, stomach pain
- fluid retention (oedema) in the lower legs, weight increase
- cough, shortness of breath
- low white blood cell counts shown by blood tests (neutropenia, leucopenia)
- abnormal liver function tests (increased transaminases)
- increased bilirubin shown by blood tests.

Uncommon side effects:

These may affect up to 1 in every 100 users

- diverticulitis (fever, nausea, diarrhoea, constipation, stomach pain)
- red swollen areas in the mouth
- high blood fat (triglycerides)
- stomach ulcer
- kidney stones
- underactive thyroid.

Very rare side effects:

These may affect up to 1 in every 10,000 users

- low counts for white blood cells, red blood cells and platelets in blood tests.
- stevens-johnson syndrome (skin rash, which may lead to severe blistering and peeling of the skin)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

Children with sJIA

In general, side effects in sJIA patients were of a similar type to those in adults with RA. Some side effects were seen more often: inflamed nose and throat, diarrhoea, lower white blood cell counts and higher liver enzymes.

Children with pJIA

In general, side effects in pJIA patients were of a similar type to those in adults with RA. Some side effects were seen more often: inflamed nose and throat, headache, feeling sick (nausea) and lower white blood cell counts. .

5. How to store RoActemra

Keep RoActemra out of the sight and reach of children.

Store in a refrigerator (2°C to 8°C). Do not freeze.

Keep the vial in the outer carton in order to protect from light.

Do not use this medicine after the expiry date which is stated on the carton.

6. Contents of the pack and other information

What RoActemra contains

- The active substance is tocilizumab.
Each 4 ml vial contains 80 mg tocilizumab (20 mg/ml).
Each 10 ml vial contains 200 mg tocilizumab (20 mg/ml).
Each 20 ml vial contains 400 mg tocilizumab (20 mg/ml).
- The other ingredients are sucrose, polysorbate 80, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate and water for injections.

What RoActemra looks like and contents of the pack

RoActemra is a concentrate for solution for infusion. The concentrate is a clear to opalescent, colourless to pale yellow liquid.

RoActemra is supplied as vials containing 4 ml, 10 ml and 20 ml concentrate for solution for infusion. Pack size of 1 and 4 vials. Not all pack sizes may be marketed.

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This leaflet was last revised

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu/>. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

Instructions for dilution prior to administration

Parenteral medicinal products should be inspected visually for particulate matter or discoloration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted.

RA adult patients

Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection from a 100 ml infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (0.4 ml/kg) should be withdrawn from the vial and placed in the 100 ml infusion bag. This should be a final volume of 100 ml. To mix the solution, gently invert the infusion bag to avoid foaming.

Use in the paediatric population

sJIA and pJIA patients \geq 30 kg

Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection from a 100 ml infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.4 ml/kg**) should be withdrawn from the vial and placed in the 100 ml infusion bag. This should be a final volume of 100 ml. To mix the solution, gently invert the infusion bag to avoid foaming.

sJIA patients < 30 kg

Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection from a 50 ml infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.6 ml/kg**) should be withdrawn from the vial and placed in the 50 ml infusion bag. This should be a final volume of 50 ml. To mix the solution, gently invert the infusion bag to avoid foaming.

pJIA patients < 30 kg

Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection from a 50 ml infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.5 ml/kg**) should be withdrawn from the vial and placed in the 50 ml infusion bag. This should be a final volume of 50 ml. To mix the solution, gently invert the infusion bag to avoid foaming.

RoActemra is for single-use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

RoActemra 162 mg solution for injection in pre-filled syringe Tocilizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it onto others. It may harm them even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

In addition to this leaflet, you will be given a **Patient Alert Card**, which contains important safety information that you need to be aware of before and during treatment with RoActemra.

What is in this leaflet:

1. **What RoActemra is and what it is used for**
2. **What you need to know before you use RoActemra**
3. **How to use RoActemra**
4. **Possible side effects**
5. **How to store RoActemra**
6. **Contents of the pack and other information**

1. What RoActemra is and what it is used for

RoActemra contains the active substance tocilizumab, which is a protein made from specific immune cells (monoclonal antibody), that blocks the action of a specific protein (cytokine) called interleukin-6. This protein is involved in inflammatory processes of the body, and blocking it can reduce the inflammation in your body. RoActemra is used to treat:

- **adults with moderate to severe active rheumatoid arthritis (RA)**, an autoimmune disease, if previous therapies did not work well enough.
- **adults with severe, active and progressive rheumatoid arthritis (RA)**, who have not had previous treatment with methotrexate.
RoActemra helps to reduce RA symptoms such as pain and swelling in your joints, and can also improve your performance of daily tasks. RoActemra has been shown to slow the damage to the cartilage and bone of the joints caused by the disease and to improve your ability to do normal daily activities.

RoActemra is usually given in combination with another medicine for RA called methotrexate. However, RoActemra can be given alone if your doctor determines that methotrexate is inappropriate.
- **adults with a disease of the arteries called giant cell arteritis (GCA)**, caused by inflammation of the body's largest arteries, especially those that supply blood to the head and neck. Symptoms include headache, fatigue and jaw pain. Effects can include strokes and blindness.

RoActemra can reduce pain and swelling in the arteries and veins in your head, neck and arms.

GCA is often treated with medicines called steroids. They are usually effective, but can have side effects if used at high doses for a long time. Reducing the steroid dose can also lead to a flare-up of the GCA. Adding RoActemra to the treatment means that steroids can be used for a shorter time, while still controlling GCA.

2. What you need to know before you use RoActemra

Do not use RoActemra

- if you are allergic to tocilizumab or any of the other ingredients of this medicine (listed in section 6).
- if you have an active, severe infection.

If either of these applies to you, tell a doctor. Do not use RoActemra.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using RoActemra.

- If you experience **allergic reactions** such as chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips, tongue, face or skin itching, hives or rash during or after the injection, then **tell your doctor immediately**.
- Do not take the next dose until you have informed your doctor AND your doctor has told you to take the next dose if you have experienced any allergic reaction symptoms after RoActemra administration.
- If you have any kind of **infection**, short- or long-term, or if you often get infections. **Tell your doctor immediately** if you feel unwell. RoActemra can reduce your body's ability to respond to infections and may make an existing infection worse or increase the chance of getting a new infection.
- If you have had **tuberculosis**, tell your doctor. Your doctor will check for signs and symptoms of tuberculosis before starting RoActemra. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever) or any other infection appear during or after therapy tell your doctor immediately.
- If you have had **intestinal ulcers** or **diverticulitis**, tell your doctor. Symptoms would include abdominal pain and unexplained changes in bowel habits with a fever.
- If you have **liver disease**, tell your doctor. Before you use RoActemra, your doctor may do a blood test to measure your liver function.
- **If any patient has recently been vaccinated**, or is planning a vaccination, tell your doctor. All patients should be up-to-date with all their vaccinations before they start treatment with RoActemra. Certain types of vaccines should not be given while receiving RoActemra.
- If you have **cancer**, tell your doctor. Your doctor will have to decide if you can still be given RoActemra.
- If you have **cardiovascular risk factors** such as raised blood pressure and raised cholesterol levels, tell your doctor. These factors need to be monitored while receiving RoActemra.
- If you have moderate to severe **kidney function problems**, your doctor will monitor you.
- If you have **persistent headaches**.

Your doctor will perform a blood test before you receive RoActemra, to determine if you have a low white blood cell count, low platelet count or high liver enzymes.

Children and adolescents

RoActemra subcutaneous injection is not recommended for use in children under 18 years of age.

Other medicines and RoActemra

Tell your doctor if you are taking any other medicines, or have recently taken any. RoActemra can affect the way some medicines work, and the dose of these may require adjustment. If you are using medicines containing any of the following active substances, **tell your doctor:**

- methylprednisolone, dexamethasone, used to reduce inflammation
- atorvastatin, used to reduce cholesterol levels
- calcium channel blockers (e.g. amlodipine), used to treat raised blood pressure
- theophylline, used to treat asthma
- warfarin or phenprocoumon, used as a blood thinning agents
- phenytoin, used to treat convulsions
- ciclosporin, used to suppress your immune system during organ transplants
- benzodiazepines (e.g. temazepam), used to relieve anxiety

Due to lack of clinical experience, RoActemra is not recommended for use with other biological medicines for the treatment of RA or GCA.

Pregnancy, breast-feeding and fertility

RoActemra is not to be used in pregnancy unless clearly necessary. Talk to your doctor if you are pregnant, may be pregnant, or intend to become pregnant.

Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

Stop breast-feeding if you are to be given RoActemra, and talk to your doctor. Leave a gap of at least 3 months after your last treatment before you start breast-feeding. It is not known whether RoActemra is passed into breast milk.

Driving and using machines

This medicine can cause dizziness. If you feel dizzy, do not drive or use machines.

3. How to use RoActemra

Always use this medicine exactly as your doctor, pharmacist or nurse has told you. You should check with your doctor, pharmacist or nurse if you are not sure.

The treatment will be prescribed and started by healthcare professionals experienced in the diagnosis and treatment of RA or GCA.

The recommended dose

The dose for all adults is 162 mg (the content of 1 pre-filled syringe) given once a week.

RoActemra is given by injection under the skin (*subcutaneously*). At the start, your doctor or nurse may inject RoActemra. However, your doctor may decide that you may inject RoActemra yourself. In this case you will get training on how to inject RoActemra yourself.

Talk to your doctor if you have any questions about giving yourself an injection. You will find detailed “Instructions for administration” at the end of this leaflet.

If you use more RoActemra than you should

Because RoActemra is given in one pre-filled syringe, it is unlikely that you will receive too much. However, if you are worried, talk to your doctor, pharmacist or nurse.

If you forget to use RoActemra

It is very important to use RoActemra exactly as prescribed by your doctor. Keep track of your next dose. If you miss your weekly dose within 7 days, take your dose on the next scheduled day. If you miss your once every other weekly dose within 7 days, inject a dose as soon as you remember and take your next dose at your regular scheduled time. If you miss your weekly or once every other weekly dose more than 7 days or are not sure when to inject RoActemra, call your doctor or pharmacist.

If you stop using RoActemra

You should not stop using RoActemra without discussing with your doctor first.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, RoActemra can cause side effects, although not everybody gets them. Side effects could occur 3 months or more after your last dose of RoActemra.

Possible serious side effects: tell a doctor straight away.

These are common: they may affect up to 1 in every 10 users

Allergic reactions during or after injection:

- difficulty with breathing, chest tightness or light-headedness
- rash, itching, hives, swelling of the lips, tongue or face

If you notice any of these, tell your doctor **immediately**.

Signs of serious infections:

- fever and chills
- mouth or skin blisters
- stomach ache

If you notice any of these, tell your doctor **as soon as possible**.

Very common side effects:

These may affect 1 in 10 patients or more

- upper respiratory tract infections with typical symptoms such as cough, blocked nose, runny nose, sore throat and headache,
- high blood fat (*cholesterol*) levels.

Common side effects:

These may affect up to 1 in 10 patients

- lung infection (pneumonia)
- shingles (herpes zoster)
- cold sores (oral herpes simplex), blisters
- skin infection (cellulitis) sometimes with fever and chills
- rash and itching, hives
- allergic (hypersensitivity) reactions
- eye infection (conjunctivitis)
- headache, dizziness, high blood pressure
- mouth ulceration, stomach pain
- fluid retention (oedema) in the lower legs, weight increase

- cough, shortness of breath
- low white blood cell counts shown by blood tests (neutropenia, leucopenia)
- abnormal liver function tests (increased transaminases)
- increased bilirubin shown by blood tests
- injection site reactions.

Uncommon side effects:

These may affect up to 1 in every 100 patients

- diverticulitis (fever, nausea, diarrhoea, constipation, stomach pain)
- red swollen areas in the mouth
- high blood fat (triglycerides)
- stomach ulcer
- kidney stones
- underactive thyroid.

Very rare side effects:

These may affect up to 1 in every 10,000 patients

- Stevens-Johnson syndrome (skin rash, which may lead to severe blistering and peeling of the skin)

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store RoActemra

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pre-filled syringe label and carton (EXP). The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C). Do not freeze.

Keep the pre-filled syringes in the outer carton in order to protect from light and moisture.

Once removed from the refrigerator, RoActemra must be administered within 8 hours and should not be kept above 30°C.

Do not use if the medicine is cloudy or contains particles, is any colour besides colourless to yellowish, or any part of the pre-filled syringe appears to be damaged.

The syringe should not be shaken. After removing the cap the injection must be started within 5 minutes to prevent the medicine from drying out and blocking the needle. If the pre-filled syringe is not used within 5 minutes of cap removal, you must dispose of it in a puncture resistant container and use a new pre-filled syringe.

If following insertion of the needle, you cannot depress the plunger, you must dispose of the pre-filled syringe in a puncture resistant container and use a new pre-filled syringe.

6. Contents of the pack and other information

What RoActemra contains

- The active substance is tocilizumab.
Each pre-filled syringe contains 162 mg tocilizumab in 0.9 ml.
- The other ingredients are L-Histidine, L-Histidine monohydrochloride monohydrate, L-Arginine, L-Arginine hydrochloride, L-Methionine, Polysorbate 80 and Water for injections.

What RoActemra looks like and contents of the pack

RoActemra is a solution for injection. The solution is colourless to slightly yellowish.

RoActemra is supplied as a 0.9 ml pre-filled syringe containing 162 mg tocilizumab solution for injection.

Each pack contains 4 pre-filled syringes **with multipacks containing 12 (3 packs of 4) pre-filled syringes. Not all pack sizes may be marketed.**

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Lietuva

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This leaflet was last revised**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency website:

<http://www.ema.europa.eu/>.

What do I need to know to use my RoActemra pre-filled syringe safely?

It is important to read, understand and follow these instructions so that you or your caregiver uses the RoActemra syringe correctly. These instructions do not replace training from your healthcare provider. Your healthcare provider should show you how to prepare and inject properly before you use the RoActemra syringe for the first time. Ask your healthcare provider any questions you may have. Do not attempt to administer an injection until you are sure that you understand how to use the RoActemra syringe.

Please also read the Patient Leaflet that comes with the RoActemra syringe for the most important information you need to know about the medicine. It is important to remain under your healthcare provider's care while using RoActemra.

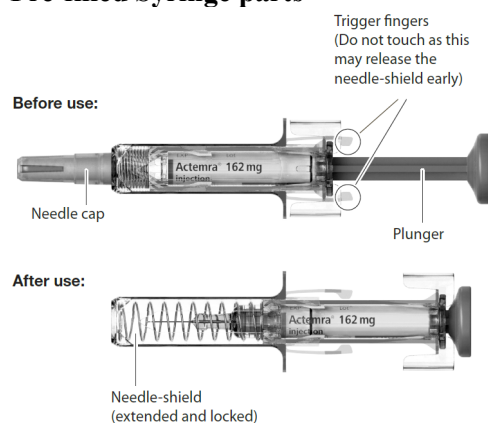
Important Information:

- Do not use the syringe if it appears to be damaged
- Do not use if medicine is cloudy, hazy, discolored or contains particles
- Do not try to take apart the syringe at any time
- Do not remove the needle-cap until you are ready to inject
- Do not inject through clothing covering the skin
- Never re-use the same syringe
- Do not touch the syringe trigger fingers as this may damage the syringe

Storage

Keep the RoActemra syringe and all medicines out of the sight and reach of children. Always store the syringe in a refrigerator at a temperature of 2-8°C. Protect the syringe from freezing and from light. Keep the pre-filled syringes in the outer carton to protect it from light and keep them dry.

Pre-filled Syringe parts



You will need the following to give your injection:

Included in the box:

- Pre-filled Syringe

Not included in the box:

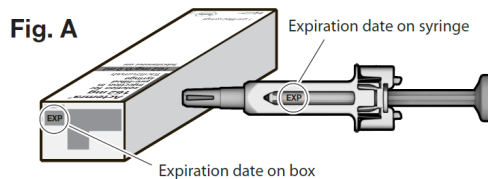
- Alcohol pad
- Sterile cotton ball or gauze
- Puncture-resistant container or sharps container for safe disposal of needle-cap and used syringe

A place to prepare your supplies:

- **Find a well-lit, clean, flat surface such as a table**

Step 1. Visually check the syringe

- Take the box containing the syringe out of the refrigerator and open the box. Do not touch the trigger fingers on the syringe as this may damage the syringe.
- Remove the syringe from the box and visually examine the syringe, as well as the medicine in the syringe. This is important to ensure that the syringe and medicine are safe to use.
- Check the expiration date on the box and syringe (See Fig. A) to make sure that it has not passed (expired). Do not use the syringe if the expiration date has passed. This is important to ensure that the syringe and medicine are safe to use.



Dispose of the syringe and do not use if:

- the medicine is cloudy
- the medicine contains particles
- the medicine is any color besides colorless to yellowish
- any part of the syringe appears to be damaged

Step 2. Allow the syringe to adjust to room temperature

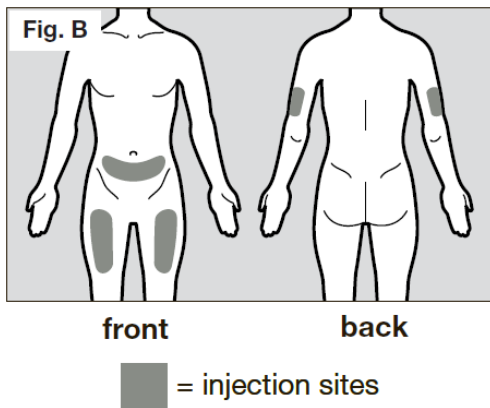
- Do not remove the needle-cap on your syringe until Step 5. Early removal of the needle-cap can cause the medication to dry out and block the needle.
- Place the syringe on a clean flat surface and allow the syringe to come to room temperature for about 25-30 minutes to warm up. Not allowing the syringe to come to room temperature could result in an uncomfortable injection and it may be difficult to depress the plunger.
- Do not warm up the syringe in any other way.

Step 3. Clean your hands

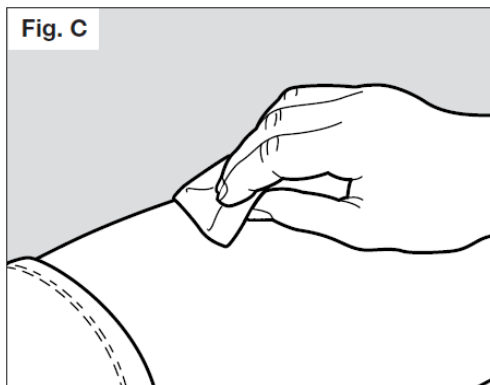
- Wash your hands with soap and water.

Step 4. Choose and prepare an injection site

- The recommended injection sites are the front and middle of your thighs and the lower part of the abdomen below the navel (belly button) except for the five centimeter area directly around the navel. (See Fig. B)
- If a caregiver is giving the injection, the outer area of the upper arms may also be used. (See Fig. B)



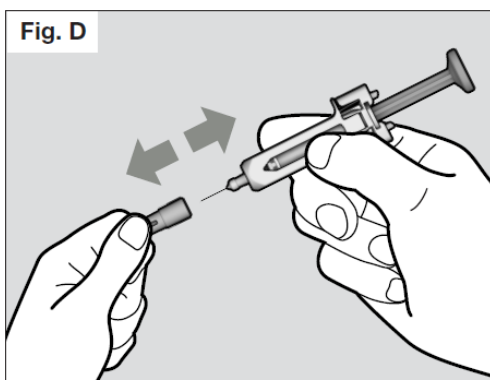
- You should use a different place each time you give yourself an injection, at least three centimeters from the area you used for your previous injection.
- Do not inject into areas that could be bothered by a belt or waistband. Do not inject into moles, scars, bruises, or areas where the skin is tender, red, hard or not intact.
- Clean the chosen injection site area using the alcohol pad (See Fig. C), to reduce the risk of infection.



- Let the skin dry for approximately 10 seconds.
- Be sure not to touch the cleaned area prior to the injection. Do not fan or blow on the clean area.

Step 5. Remove needle-cap

- Do not hold the syringe by the plunger while removing the needle-cap.
- Hold the needle-shield of the syringe firmly with one hand and pull off the needle-cap with the other hand. (See Fig. D) If you cannot remove the needle cap you should request the help of a caregiver or contact your healthcare provider.



- Do not touch the needle or let it touch any surface.

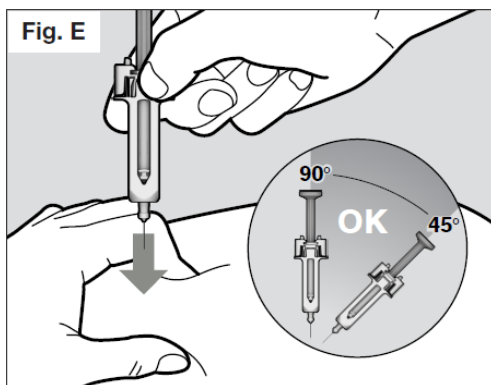
- You may see a drop of liquid at the end of the needle. This is normal.
- Throw away the needle-cap in the puncture resistant container or sharps container.

NOTE: Once the needle-cap is removed, the syringe must be used immediately.

- If it is not used within 5 minutes of cap removal, the syringe must be disposed of in the puncture resistant container or sharps container and a new syringe must be used. If the needle cap is removed for more than 5 minutes, it may be more difficult to perform an injection as the medicine can dry out and block the needle.
- Never reattach the needle-cap after removal.

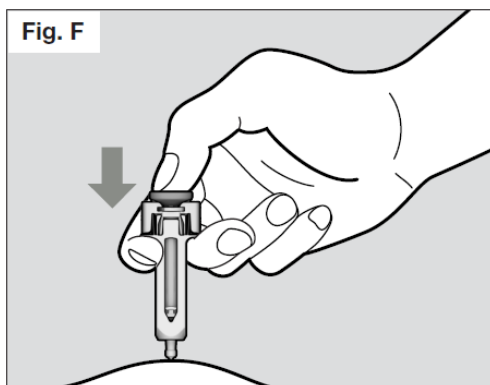
Step 6. Give the injection

- Hold the syringe comfortably in your hand.
- To be sure the needle can be inserted correctly under the skin, pinch a fold of loose skin at the clean injection site with your free hand. Pinching the skin is important to ensure that you inject under the skin (into fatty tissue) but not any deeper (into muscle). Injection into muscle could result in an uncomfortable injection.
- Do not hold or push on the plunger while inserting the needle into the skin.
- Insert the needle all the way into the pinched skin at an angle between 45° to 90° with a quick, firm action. (See Fig. E).

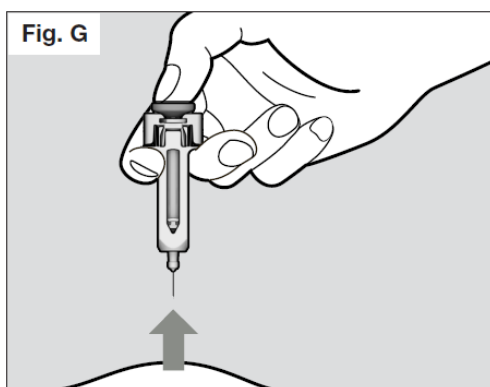


It is important to choose the correct angle to ensure the medication is delivered under the skin (into fatty tissue), otherwise the injection could be painful and the medication may not work.

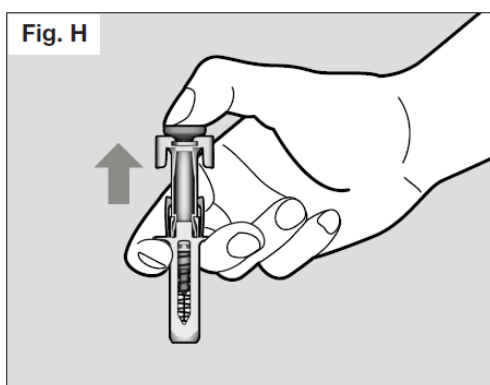
- Then keep the syringe in position and let go of the pinch of skin.
- Slowly inject all of the medicine by gently pushing the plunger all the way down. (See Fig. F). You must press the plunger all the way down to ensure that you get the full dose of medication and to ensure the trigger fingers are completely pushed to the side. If the plunger is not fully depressed the needle shield will not extend to cover the needle when it is removed. If the needle is not covered proceed carefully, and place the syringe into the puncture resistant container to avoid injury with the needle.



- Once the plunger is pushed all the way down, keep pressing down on the plunger to be sure all of the medicine is injected before taking the needle out of the skin.
- Keep pressing down on the plunger while you take the needle out of the skin at the same angle as inserted. (See Fig. G)
- If following insertion of the needle, you cannot press down the plunger, you must dispose of the pre-filled syringe in a puncture resistant container and use a new pre-filled syringe (starting again at Step 2). If you still experience difficulty, you should consult your healthcare provider.



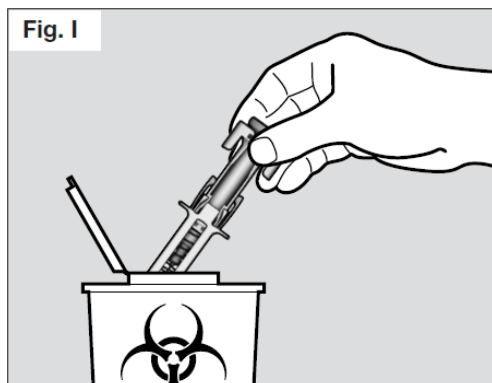
- Once the needle is removed completely from the skin, you can release the plunger, allowing the needle-shield to protect the needle. (See Fig. H)



- If you see drops of blood at the injection site, you can press a sterile cotton ball or gauze over the injection site for approximately 10 seconds.
- Do not rub the injection site.

Step 7. Dispose of the syringe

- Do not try to re-cap your syringe.
- Throw away used syringes in a puncture-resistant container or sharps container. Ask your healthcare provider or pharmacist for information about where you can get a "sharps" container or what other types of puncture-resistant containers you can use to safely dispose of your used syringes, if you do not have one. (See Fig. I)



Check with your healthcare provider for instructions about the right way to throw away used syringes. There may be local or state laws about how to throw away used syringes.

Do not throw away used syringes or the puncture resistant container in household trash and do not recycle them.

- Dispose of the full container as instructed by your healthcare provider or pharmacist.
- Always keep the puncture-resistant container out of the sight and reach of children.

Patient advice regarding hypersensitivity reactions (also known as anaphylaxis, if severe)

If you develop symptoms such as, but not limited to skin rash, itching, chills, swelling of face, lips, tongue or throat, chest pain, wheezing, difficulty breathing or swallowing or feeling dizzy or faint at any time while not at the clinic during or following an RoACTEMRA injection you should seek emergency care immediately.

Patient advice regarding early recognition and treatment to limit risk of a serious infection

Be alert for the first signs of infection such as:

- body aches, fever, chills
- cough, chest discomfort/tightness, shortness of breath
- redness, heat, unusual swelling of skin or joint
- abdominal pain/tenderness and/or change in bowel function

Call your doctor and seek medical attention without delay if you think you might be developing an infection.

If you have any concerns or questions about your syringe, contact your healthcare provider or pharmacist for assistance.