

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:

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 a 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 moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. RoActemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with 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.

4.2 Posology and method of administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA or sJIA. 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)	Dose modify concomitant MTX if appropriate 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 Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate
> 3 to 5 x ULN (confirmed by repeat testing, see section 4.4).	Interrupt RoActemra dosing until < 3 x ULN and follow recommendations above for > 1 to 3 x ULN For persistent increases > 3 x ULN, discontinue RoActemra
> 5 x ULN	Discontinue RoActemra

- 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 > $1 \times 10^9/l$ resume RoActemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
ANC < 0.5	Discontinue RoActemra

- Low platelet count

Laboratory Value (cells x $10^3/\mu l$)	Action
50 to 100	Interrupt RoActemra dosing When platelet count > $100 \times 10^3/\mu l$ 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 safety and efficacy of RoActemra in patients below 2 years of age has not been established. No data are available.

The recommended posology 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.

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 effect laboratory values in sJIA, ~~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	Dose modify concomitant MTX if appropriate For persistent increases in this range, interrupt RoActemra until ALT/AST have normalized.
> 3 x ULN to 5x ULN	Dose modify 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.
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- Low platelet count

Laboratory Value (cells x 10 ³ /μl)	Action
50 to 100	Dose modify 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.

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 and sJIA patients should be administered as an intravenous infusion over 1 hour.

RA Patients, and SJIA 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 further information on dilution prior to administration, see section 6.6.

SJIA 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 further information on dilution prior to administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including RoActemra (see section 4.8, Undesirable Effects). RoActemra treatment should 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) 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 or sJIA 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 who may be less able to communicate their symptoms) and parents/guardians of sJIA 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 and sJIA patients should be screened for latent tuberculosis (TB) infection prior to starting RoActemra therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating RoActemra.

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 x ULN. In patients with baseline ALT or AST > 5 x 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 > 3–5 x ULN, confirmed by repeat testing, RoActemra treatment should be interrupted.

In sJIA 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 $2 \times 10^9/l$. Caution should be exercised when considering initiation of RoActemra treatment in patients with a low platelet count (i.e. platelet count below $100 \times 10^3/\mu l$). In patients who develop an ANC < $0.5 \times 10^9/l$ or a platelet count < $50 \times 10^3/\mu l$, 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 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 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. It is recommended that all patients, particularly sJIA patients, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating RoActemra therapy. The interval between live vaccinations and initiation of RoActemra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

Cardiovascular risk

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 or sJIA 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'.

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

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. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses may need to be increased to maintain therapeutic effect. Given its long elimination half-life ($t_{1/2}$), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

4.6 Fertility, pregnancy and lactation

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

RoActemra should not be used during pregnancy unless clearly necessary.

Lactation

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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, given that dizziness has been commonly reported, patients who experience this adverse reaction should be advised not to drive or use machines until it has resolved.

4.8 Undesirable effects

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 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 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 $< 1/10$) or uncommon ($\geq 1/1,000$ to $< 1/100$). 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.

Gastrointestinal Perforation

During the six 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 6/3,778 patients, 0.2%) was several fold higher with the 4 mg/kg dose, compared to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported in a total of 13 out of 3,778 patients (0.3%) 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. It is not clear if the infections were related to neutropenia.

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 six 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.

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.

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. 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 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.

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.

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

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

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 \geq 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 1196 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 2). 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 (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 tocilizumab 8 mg/kg plus DMARD than in patients receiving tocilizumab 4 mg/kg plus DMARD ($p < 0.0001$).

Table 2. ACR responses in placebo-/MTX-/DMARDs-controlled studies (% patients)

Week	Study I AMBITION		Study II LITHE		Study III OPTION		Study IV TOWARD		Study V RADIATE	
	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
 * - $p < 0.05$, TCZ vs. PBO + MTX/DMARD
 ** - $p < 0.01$, 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 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 tocilizumab 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

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.

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 4.

Table 4. 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%

¹p<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 < 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).

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 in one or more subsets of the paediatric population in juvenile idiopathic arthritis. See 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

RA Patients

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 1,793 RA patients treated with a one-hour infusion of 4 and 8 mg/kg tocilizumab every 4 weeks 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) = 35000 ± 15500 h $\mu\text{g/ml}$, trough concentration (C_{\min}) = 9.74 ± 10.5 $\mu\text{g/ml}$ and maximum concentration (C_{\max}) = 183 ± 85.6 $\mu\text{g/ml}$, and the accumulation ratios for AUC and C_{\max} were small, 1.22 and 1.06, respectively. The accumulation ratio was higher for C_{\min} (2.35), 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 $55500 \pm 14100 \mu\text{g}\cdot\text{h/mL}$, $19.0 \pm 12.0 \mu\text{g/mL}$, and $269 \pm 57 \mu\text{g/mL}$, respectively, which are higher than mean exposure values for the patient population ($\text{AUC} = 35000 \pm 15500 \text{ h } \mu\text{g/ml}$, $C_{\min} = 9.74 \pm 10.5 \mu\text{g/ml}$ and $C_{\max} = 183 \pm 85.6 \mu\text{g/ml}$). 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 $> 800 \text{ mg}$ 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 3.5 l , the peripheral volume of distribution was 2.9 l resulting in a volume of distribution at steady state of 6.4 l .

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 12.5 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 14 days to 8 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 2.7 and 6.5 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 $< 80 \text{ ml/min}$ and $\geq 50 \text{ ml/min}$) 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 $\geq 30 \text{ kg}$) or 12 mg/kg (patients with a body weight $< 30 \text{ kg}$), given every 2 weeks. The predicted mean ($\pm \text{SD}$) $\text{AUC}_{2\text{weeks}}$, C_{\max} and C_{\min} of tocilizumab were $32200 \pm 9960 \mu\text{g}\cdot\text{hr/ml}$, $245 \pm 57.2 \mu\text{g/ml}$ and $57.5 \pm 23.3 \mu\text{g/ml}$, 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 $\geq 30 \text{ kg}$ or 12 mg/kg for body weight $< 30 \text{ kg}$) at week 12.

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 x 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.

RoActemra is supplied as a sterile concentrate that does not contain preservatives.

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 discoloration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted

RA Patients, and SJIA 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.

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/RENEWAL OF THE AUTHORISATION

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 OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURING AUTHORISATION
HOLDER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER 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

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

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

• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

The Marketing Authorisation Holder (MAH) shall provide an educational pack covering the therapeutic indications RA and sJIA, 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 and sJIA patients), preparation of infusion and infusion rate
- Risk of serious infections
 - The product should not be given to patients with active or suspected infection
 - The product may lessen signs and symptoms of acute infection delaying the diagnosis
- Serious 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 patients

The Nurse Information Pack should contain the following key elements:

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

The Patient Information Pack should contain the following key elements:

- Patient Information Leaflet
- 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.

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation is in place and functioning before and whilst the product is on the market.

Risk Management plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 12.0 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

The Marketing Authorisation Holder will submit PSURs at 6-monthly intervals, unless otherwise specified by the CHMP.

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 reach and sight 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

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 reach and sight 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

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 reach and sight 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**

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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

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

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 start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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.

In this leaflet:

1. What RoActemra is and what it is used for
2. Before you use RoActemra
3. How to use RoActemra
4. Possible side effects
5. How to store RoActemra
6. Further information

1. WHAT ROACTEMRA IS AND WHAT IT IS USED FOR

RoActemra contains the active substance tocilizumab, a 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. 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 usually given in combination with methotrexate. However, RoActemra can be given alone if your doctor determines that methotrexate is inappropriate.

RoActemra is also used to treat patients 2 years of age and older with 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.

2. BEFORE YOU USE ROACTEMRA

Do not use RoActemra

- if you are allergic (hypersensitive) to tocilizumab or any of the other ingredients of RoActemra (listed in section 6, 'What RoActemra contains').
- if you have an active, severe infection.

Take special care with 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 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 examine your liver function.
- If you have recently got or are planning to get vaccinated, tell your doctor. Certain types of vaccines should not be given while receiving RoActemra. It is recommended that all patients, particularly sJIA patients, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating RoActemra therapy.
- If you have a history of macrophage activation syndrome, tell your doctor. Your doctor will have to decide if you can still be given 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.

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.

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

Using other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. RoActemra can affect the way some medicines work, and the dose of these may require adjustment. You and parents/guardians of sJIA patients, should tell your doctor if you are using medicines containing any of the following active substances:

- atorvastatin, used to reduce cholesterol levels
- calcium channel blockers (e.g. amlodipine), used to treat raised blood pressure
- theophylline, used to treat asthma
- warfarin, used as a blood thinning agent
- 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 sJIA.

Pregnancy and breast-feeding

Talk to your doctor if you are pregnant, may be pregnant, intend to become pregnant or if you are breast-feeding. Women of childbearing potential must use effective contraception during and up to 3 months after treatment. RoActemra should not be used during pregnancy unless clearly necessary.

It is not known whether RoActemra is excreted in breast milk. If you are a nursing mother, you should stop breast-feeding if you are to be given RoActemra. Before starting breast-feeding, your last treatment with RoActemra should be at least 3 months ago.

Driving and using machines

There are no studies on the effects of RoActemra on the ability to drive and use machines. However, if you experience dizziness, a common side effect, then you should not drive or use machines.

Important information about some of the ingredients of RoActemra

This medicinal product contains 26.55 mg sodium per maximum dose of 1200 mg (8.85 mg sodium per 400 mg vial). 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'.

3. HOW TO USE ROACTEMRA

RA Patients

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.

You will receive RoActemra once every 4 weeks through a drip in your vein (intravenous infusion) over one hour.

SJIA Patients

The usual dose of RoActemra is 8 mg per kg of body weight if you weigh 30 kg or more or 12 mg per kg of body weight if you weigh less than 30 kg, calculated based on your body weight at each administration.

You will receive RoActemra once every 2 weeks through a drip in your vein (intravenous infusion) over one hour.

After dilution, RoActemra will be given to you by a doctor or nurse, who will also monitor you during and after administration.

If you use 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 forget to use 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.

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 RoActemra, then please ask your doctor or pharmacist.

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.

The most common side effects of RoActemra are upper respiratory tract infections, with typical symptoms such as cough, blocked nose, runny nose, sore throat and headache.

Possible serious side effects include serious infections and allergic (hypersensitivity) reactions, that may, in a small number of cases, be life-threatening.

If you notice any of the following signs of:

allergic reactions during or after infusion, tell your doctor **immediately**:

- difficulty with breathing or light-headedness
- rash, itching, hives, swelling of the lips.

infections, tell your doctor **as soon as possible**:

- fever and chills
- mouth or skin blisters
- stomach ache
- persistent headaches.

The symptoms described above can be signs of the side effects listed below, all of which have been observed with RoActemra in clinical studies.

Side effects may occur with certain frequencies, which are defined as follows:

- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

Very common side effects: upper respiratory tract infections like coughs and colds, and high cholesterol levels.

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

Uncommon side effects: diverticulitis (fever, nausea, diarrhoea, constipation, stomach pain), red swollen (inflamed) areas in the mouth, high blood fat (triglycerides), stomach ulcer, kidney stones and underactive thyroid.

Very rare side effects: low blood measurements for white blood cells, red blood cells and platelet count.

SJIA Patients

In general, the side effects in sJIA patients were similar in type to those seen in RA patients as stated above.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ROACTEMRA

Keep out of the reach and sight of children.

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

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

6. FURTHER 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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Manufacturer

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This leaflet was last approved

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

The following information is intended for medical or 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 Patients, and SJIA 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.

RoActemra is for single-use only.

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