The content of this leaflet was updated according to the guidelines of the Ministry of Health.

Actemra 20mg/ml I.V.®

TOCILIZUMAB

Concentrate for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT

Actemra 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

Actemra (tocilizumab), is indicated for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who had an inadequate response to one or more DMARDs(Disease Modifying Anti-Rheumatic Drugs) or TNF antagonists or in whom DMARDs cannot be used. Actemra can be used alone or in combination with methotrexate or other DMARDs.

Actemra 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.

Actemra is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older.

Actemra in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (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.

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

Actemra in combination with methotrexate (MTX) in indicated for the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.

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.

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)	Modify the dose of the concomitant MTX if appropriate For persistent increases in this range, reduce Actemra dose to 4 mg/kg or interrupt Actemra 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 Actemra dosing until < 3 x ULN and follow recommendations above for > 1 to 3 x ULN For persistent increases > 3 x ULN, discontinue Actemra
> 5 x ULN	Discontinue Actemra

- Low absolute neutrophil count (ANC)

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

Laboratory Value (cells x 10^9/ l)	Action
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt Actemra dosing

	When ANC increases > 1 x 10^9/ l resume Actemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
ANC < 0.5	Discontinue Actemra

- Low platelet count

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

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 Actemra 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 Actemra until ALT/AST have normalized.
> 3 x ULN to 5x ULN	Modify the dose of the concomitant MTX if appropriate Interrupt Actemra dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN
> 5x ULN	Discontinue Actemra. The decision to discontinue Actemra 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 10^9/ l)	**Action**
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt Actemra dosing When ANC increases to > 1 x 10^9/ l resume Actemra
ANC < 0.5	Discontinue Actemra The decision to discontinue Actemra in sJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low platelet count

Laboratory Value (cells x 10^3/µl)	**Action**
50 to 100	Modify the dose of the concomitant MTX if appropriate Interrupt Actemra dosing When platelet count is > 100 x 10^3/µl resume Actemra
< 50	Discontinue Actemra. The decision to discontinue Actemra 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 Actemra. 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 Actemra 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 Actemra until ALT/AST have normalized.
> 3 x ULN to 5x ULN	Modify the dose of the concomitant MTX if appropriate Interrupt Actemra dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN
> 5x ULN	Discontinue Actemra. The decision to discontinue Actemra 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 10^9/ l)	**Action**
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt Actemra dosing When ANC increases to > 1 x 10^9/ l resume Actemra
ANC < 0.5	Discontinue Actemra The decision to discontinue Actemra in pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low platelet count

Laboratory Value (cells x 10^3/µl)	**Action**
50 to 100	Modify the dose of the concomitant MTX if appropriate Interrupt Actemra dosing When platelet count is > 100 x 10^3/µl resume Actemra
< 50	Discontinue Actemra. The decision to discontinue Actemra 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 Actemra. 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. Actemra 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
Actemra has not been studied in patients with hepatic impairment. Therefore, no dose recommendations can be made.

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

RA, sJIA and pJIAPatients ≥ 30 kg
Actemra 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
Actemra 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

Infections
Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including Actemra (see section 4.8, Undesirable Effects). Actemra treatment must not be initiated in patients with active infections (see section 4.3). Administration of Actemra 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 Actemra 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 Actemra therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating Actemra. 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 Actemra.

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 Actemra in RA patients (see section 4.8). Actemra 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 Actemra (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 Actemra. If an anaphylactic reaction or other serious hypersensitivity / serious infusion related reaction occurs, administration of Actemra should be stopped immediately and Actemra should be permanently discontinued.

Active hepatic disease and hepatic impairment
Treatment with Actemra, 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 Actemra 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 Actemra. When clinically indicated, other liver function tests including bilirubin should be considered.

Caution should be exercised when considering initiation of Actemra 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, Actemra 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 Actemra, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/l. Caution should be exercised when considering initiation of Actemra treatment in patients with a low platelet count (i.e. platelet count below 100 x 10^3/ µl). In patients who develop an ANC < 0.5 x 10^9/ l or a platelet count < 50 x 10^3/µl, 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 Actemra 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 Actemra 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 Actemra 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 Actemra as clinical safety has not been established. In a randomized open-label study, adult RA patients treated with Actemra 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 Actemra therapy. The interval between live vaccinations and initiation of Actemra 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 Actemra with TNF antagonists or other biological treatments for RA, sJIA or pJIA patients. Actemra 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'.

Traceability
In order to improve the traceability of biological medicinal products, the tradename and batch number of the administered product should be clearly recorded (or stated) in the patient file.

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. 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.

Actemra 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 Actemra should be made taking into account the benefit of breast-feeding to the child and the benefit of Actemra 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

Actemra 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 ≥ 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 (≥ 1/10); common (≥ 1/100 to < 1/10), uncommon (≥ 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 Actemra 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 x 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 x 10^9/ l did so within 8 weeks after starting therapy. Decreases below 0.5 x 10^9/ l were reported in 0.3% patients receiving 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 x 10^3/ µl 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 Actemra 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 toclizumab 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 see 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 (≥ 1/10); common (≥ 1/100 to < 1/10) or uncommon (≥ 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, diarrhea, 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 1×10^9/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 ≥ 3xULN 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 >1.5-2 x ULN occurred in one patient (0.5%) and elevation in LDL >1.5-2 x 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 x 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 x 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 ≤ 100 x 10^3/µl.

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

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

In the ongoing open label extension phase, elevation in ALT or AST ≥ 3 x ULN occurred in 12% and 4% of patients, respectively, in the 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 x ULN to 2 x ULN occurred in 1.5% of the tocilizumab group and none in the placebo group. Elevation in LDL > 1.5 x ULN to 2 x ULN occurred in 1.9% of patients in the 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 authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form :
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

There are limited data available on overdose with Actemra. 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 (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 DAS28 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 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≤ 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 Actemra 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)

	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

[a] *p 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 (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 (WA19926) 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 ≥ 37.5°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 ≥ 37.5°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 ($p<0.0001$).

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 1, 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 Actemra in all subsets of the paediatric population in rheumatoid arthritis and has deferred the obligation to submit the results of studies with Actemra 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 3, 552 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 ± SD) were estimated for a dose of 8 mg/kg tocilizumab given every 4 weeks: steady-state area under curve (AUC) = 38000 ± 13000 h µg/ml, trough concentration (C_{min}) = 15.9 ± 13.1 µg/ml and maximum concentration (C_{max}) = 182 ± 50.4 µg/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 (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 50000 ± 16800 µg•h/mL, 24.4 ± 17.5 µg/mL, and 226 ± 50.3 µg/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 (± SD) AUC_{2weeks}, C_{max} and C_{min} of tocilizumab were 32200 ± 9960 µg•h/mL, 245 ± 57.2 µg/ml and 57.5 ± 23.3 µg/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 (± SD) AUC_{4weeks}, C_{max} and C_{min} of tocilizumab were 29500 ± 8660 µg·hr/mL, 182 ± 37 µg/mL and 7.49 ± 8.20 µg/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 (± SD) AUC_{4weeks}, C_{max} and C_{min} of tocilizumab were 23200 ± 6100 µg·hr/mL, 175 ± 32 µg/mL and 2.35 ± 3.59 µg/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 ≥ 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 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

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 30ºC 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

Actemra is supplied in a vial (type I glass) with a stopper (butyl rubber) containing 4 ml or 10 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 Actemra concentrate required for the patients dose, under aseptic conditions. The required amount of Actemra 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 Actemra concentrate required for the patients dose, under aseptic conditions. The required amount of Actemra 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 Actemra concentrate required for the patients dose, under aseptic conditions. The required amount of Actemra 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 Actemra concentrate required for the patients dose, under aseptic conditions. The required amount of Actemra 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.

Actemra 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 Pharmaceuticals (Israel) Ltd., P.O. Box 6391, Hod Hasharon, 4524079.

8. MARKETING AUTHORISATION NUMBER(S)

142.21.31931.00

9. MANUFACTURER

F. Hoffmann-La Roche Ltd., Basel, Switzerland.

Medicine: keep out of reach of children

This prescribing information was updated on September 2017.