Actemra®
Tocilizumab

Anti-human interleukin-6 (IL-6) receptor

1. DESCRIPTION

1.1 Therapeutic/Pharmacologic Class of Drug

Tocilizumab is a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG_1 subclass.

ATC Code: L04AC07.

1.2 Type of Dosage Form

Intravenous (IV) formulation/Actemra IV: Concentrate solution for infusion.
Subcutaneous (SC) formulation/Actemra SC: Ready-to-use sterile liquid solution in a single-use prefilled syringe (PFS) with needle safety device (NSD).

1.3 Route of Administration

Intravenous (IV) infusion.
Subcutaneous (SC) injection.

1.4 Sterile/Radioactive Statement

Sterile.

1.5 Qualitative and Quantitative Composition

Active ingredients: Tocilizumab.

Actemra solution for intravenous (IV) is a clear to opalescent, colourless to pale yellow liquid, supplied in preservative-free, nonpyrogenic single-use vials, supplied in 10 mL and 20 mL vials containing 4 mL or 20 mL of tocilizumab (20 mg/mL).

Excipients with known effects:
Each 80 mg vial contains 0.10 mmol (2.21 mg) sodium.
Each 400 mg vial contains 0.39 mmol (8.85 mg) sodium.

Actemra SC is a yellowish, preservative-free liquid supplied in a ready-to-use, single-use prefilled syringe with needle safety device (PFS+NSD). Each device delivers 0.9 mL (162 mg) of tocilizumab.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Rheumatoid Arthritis (RA) [IV and SC formulation]
Actemra, in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying antirheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, Actemra can be given as monotherapy in case of intolerance to or inappropriate with MTX, DMARD, anti-TNF and other established drugs for RA. Actemra has been shown to inhibit progression of joint damage as measured by X-ray and to improve physical function when given in combination with MTX.

Polyarticular Juvenile Idiopathic Arthritis (pJIA) [IV formulation only]
Actemra IV is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older, with an inadequate response to methotrexate, due to lack of efficacy or toxicity, who were receiving standard of care, either with or without non-steroidal anti-inflammatory drugs (NSAIDs), either with or without low-dose corticosteroids, and either with or without concomitant methotrexate therapy.

Systemic Juvenile Idiopathic Arthritis (sJIA) [IV formulation only]
Actemra IV is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX or non-steroidal anti-inflammatory drugs and systemic corticosteroids.

2.2 Dosage and Administration

General
Substitution by any other biological medicinal product requires the consent of the prescribing physician.

For adult patients with RA, Actemra may be administered as an IV infusion or a SC injection.

For patients with pJIA and sJIA, Actemra is administered as an IV infusion.

Intravenous Administration
Actemra IV is not intended for subcutaneous administration.

Actemra IV should be diluted by healthcare professionals with sterile 0.9% w/v sodium chloride solution using aseptic technique (see section *4.2 Special Instructions for Use, Handling and Disposal)*. The recommended duration of IV infusion is 1 hour.

Subcutaneous Administration
Actemra SC is not intended for intravenous administration.

Actemra SC is administered with a single-use PFS + NSD. The first injection should be performed under the supervision of a qualified healthcare professional. A patient can self-inject Actemra SC only if the physician determines that it is appropriate and the patient agrees to medical follow-up as necessary and has been trained in proper injection technique. The recommended injection sites (abdomen, thigh and upper arm) should be rotated and injections should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

Patients who transition from Actemra IV therapy to Actemra SC administration should administer the first SC dose at the time of the next scheduled IV dose under the supervision of a qualified healthcare professional.

Rheumatoid Arthritis [IV and SC formulations]
Intravenous Dosing Regimen:

The recommended dose of Actemra IV for adult patients is 8 mg/kg given once every four weeks as an IV infusion.

Actemra IV can be used alone or in combination with MTX and/or other DMARDs.

For individuals whose body weight is more than 100 kilograms (kg), doses exceeding 800 mg per infusion are not recommended (see section *3.2 Pharmacokinetic Properties)*.

Subcutaneous Dosing Regimen:

The recommended dose of Actemra SC for adult patients is 162 mg given once every week as a subcutaneous injection. Actemra SC can be used alone or in combination with MTX and/or other DMARDs.

Dose Modification Recommendations for RA:
(see section *2.4.1 Warnings and Precautions, General)*

• Liver enzyme abnormalities

Lab Value	Action
> 1 to 3x ULN	Dose modify concomitant DMARDs if appropriate. For patients on Actemra SC with persistent increases in this range, reduce Actemra SC injection frequency to every other week or interrupt Actemra SC until ALT/AST have normalized. Resume Actemra at every other week and increase frequency to every week as clinically appropriate. For patients on Actemra IV with persistent increases in this range, reduce Actemra dose to 4 mg/kg or interrupt Actemra IV until ALT/AST have normalized. Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate.
> 3 to 5x ULN	Interrupt Actemra dosing until < 3x ULN and follow recommendations above for > 1 to 3x ULN. For persistent increases > 3x ULN (confirmed by repeat testing), discontinue Actemra.
> 5x ULN	Discontinue Actemra.

• Low absolute neutrophil count (ANC)

Lab Value (cells x 10^9/L)	Action
ANC > 1	Maintain dose.
ANC 0.5 to 1	Interrupt Actemra dosing. For patients on Actemra SC, when ANC > 1 x 10^9/L resume Actemra SC injection every other week and increase frequency to every week, as clinically appropriate. For patients on Actemra IV, 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

Lab Value (cells x 10^3/µL)	**Action**
50 to 100	Interrupt Actemra dosing. For patients on Actemra SC, when platelet count is > 100 x 10^3/µL resume Actemra SC injection every other week and increase frequency to every week, as clinically appropriate. For patients on Actemra IV, when platelet count is > 100 x 10^3/µL resume Actemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate.
< 50	Discontinue Actemra.

Polyarticular Juvenile Idiopathic Arthritis (pJIA) [IV formulation only]
A change in dose should only be based on a consistent change in the patient's body weight over time. Actemra IV can be used alone or in combination with MTX.

The recommended dose of Actemra IV for patients with pJIA is:
- 10 mg/kg for patients below 30 kg
- 8 mg/kg for patients ≥ 30 kg

given once every four weeks as an IV infusion.

Systemic Juvenile Idiopathic Arthritis (sJIA) [IV formulation only]
A change in dose should only be based on a consistent change in the patient's body weight over time. Actemra IV can be used in combination with MTX or non-steroidal inflammatory drugs and systemic corticosteroid.

The recommended dose of Actemra IV for patients with sJIA is:
- 12 mg/kg for patients below 30 kg
- 8 mg/kg for patients ≥ 30 kg

given once every two weeks as an IV infusion.

Dose Modification Recommendations for pJIA and sJIA:
Dose reduction of Actemra IV has not been studied in the pJIA or sJIA population. Dose interruptions of Actemra IV for laboratory abnormalities are recommended in patients with pJIA or sJIA and are similar to what is outlined above for patients with RA (also see section *2.4.1 Warnings and Precautions, General*). If appropriate, concomitant methotrexate and/or other medications should be dose modified or stopped and Actemra IV dosing interrupted until the clinical situation has been evaluated. In pJIA or sJIA, the decision to discontinue Actemra IV for a laboratory abnormality should be based upon the medical assessment of the individual patient.

2.2.1 Special Dosage Instructions
Pediatric use: The safety and efficacy in patients aged less than 2 years with Actemra IV in pJIA and sJIA have not been established.

Geriatric use: No dose adjustment is required in elderly patients > 65 years of age.

Renal impairment: No dose adjustment is required in patients with mild renal impairment (see section *3.2.5 Pharmacokinetics in Special Populations)*. Actemra has not been studied in patients

with moderate to severe renal impairment. Renal function should be monitored closely in these patients.

Hepatic impairment: The safety and efficacy of Actemra has not been studied in patients with hepatic impairment (see section *2.4.1 Warnings and Precautions, General*). Therefore, no dose recommendation can be made.

2.3 Contraindications

Actemra is contraindicated in patients with:

- a known hypersensitivity to tocilizumab or to any of the excipients.
- active, severe infection.

2.4 Warnings and Precautions

2.4.1 General

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

All indications

Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including Actemra (see section *2.6 Undesirable Effects*). Actemra treatment should not be initiated in patients with active infections. Administration of Actemra should be interrupted if a patient develops a serious infection until the infection is controlled. Healthcare professionals should exercise caution when considering the use of Actemra in patients with a history of recurring infection 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 immunosuppressive agents, such as tocilizumab, as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute phase reactants. Patients (which include younger children who may be less able to communicate their symptoms) and parents/guardians of minors with pJIA or sJIA should be instructed to contact their healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

Complications of diverticulitis

Events of diverticular perforations as complications of diverticulitis have been reported in patients treated with Actemra. 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, should be evaluated promptly for early identification of gastrointestinal perforation.

Tuberculosis

As recommended for other biological therapies, all patients should be screened for latent tuberculosis (TB) infection prior to starting Actemra therapy. Patients with latent TB should be treated with standard antimycobacterial therapy before initiating Actemra.

Vaccinations

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

No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving Actemra.

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 pediatric or elderly patients, if possible, be brought up to date with all immunizations in agreement with current immunization 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.

Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylaxis have been reported in association with Actemra (see section *2.6.1 Undesirable Effects, Clinical Trials*). In the postmarketing setting, events of serious hypersensitivity and anaphylaxis have occurred in patients treated with a range of doses of Actemra, with or without concomitant therapies, premedication, and/or a previous hypersensitivity reaction. In the postmarketing setting, cases with a fatal outcome have been reported with Actemra IV. These events have occurred as early as the first infusion of Actemra IV (see sections *2.3 Contraindications, 2.6.2 Postmarketing Experience)*. Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during infusion with Actemra IV. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of Actemra should be stopped immediately and Actemra should be permanently discontinued (see section *2.2 Dosage and Administration*).

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 *2.2.1 Special Dosage Instructions, 2.6.1 Undesirable Effects, Clinical Trials*).

Hepatotoxicity

Mild and moderate elevations of hepatic transaminases have been reported commonly with Actemra treatment (see section *2.6.1 Undesirable Effects, Clinical Trials*). Increased frequency of these elevations was observed when drugs, which are known to cause hepatotoxicity (e.g. MTX), were used in combination with Actemra.

Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, have been observed with Actemra (see section *2.6.2 Undesirable Effects, Postmarketing Experience*). Serious hepatic injury occurred between 2 weeks to more than 5 years after initiation of Actemra. Cases of liver failure resulting in liver transplantation have been reported.

Caution should be exercised when considering initiation of Actemra treatment in patients with elevated transaminases ALT or AST above 1.5 x ULN. In RA, pJIA and sJIA patients with elevated ALT or AST above 5 x ULN, treatment is not recommended.

In RA, pJIA and sJIA patients, ALT/AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended dose modifications, including Actemra discontinuation, based on transaminases levels, see section *2.2 Dosage and Administration*.

Viral reactivation

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

Demyelinating 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.

Neutropenia

Treatment with Actemra was associated with a higher incidence of neutropenia. Treatment-related neutropenia was not associated with serious infection in clinical trials (see section *2.6.1 Undesirable Effects, Clinical Trials*).

Caution should be exercised when considering initiation of Actemra treatment in patients with a low neutrophil count i.e. absolute neutrophil count (ANC) below 2 x 10^9/L. In RA, pJIA and sJIA patients with an absolute neutrophil count below 0.5 x 10^9/L treatment is not recommended.

In RA patients, the neutrophil count should be monitored 4 to 8 weeks after start of therapy and thereafter according to good clinical practice. For recommended dose modifications based on ANC results, see section 2.2 *Dosage and Administration.*

In pJIA and sJIA patients, the neutrophil count should be monitored at the time of the second infusion and thereafter according to good clinical practice (see section *2.2 Dosage and Administration, Dose Modifications*).

Thrombocytopenia

Treatment with Actemra was associated with a reduction in platelet counts. Treatment-related reduction in platelets was not associated with serious bleeding events in clinical trials (see section *2.6.1 Undesirable Effects, Clinical Trials*).

Caution should be exercised when considering initiation of Actemra treatment in patients with a platelet count below 100 x 10^3/µL. In all patients with a platelet count below 50 x 10^3/µL treatment is not recommended.

In RA patients, platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to good clinical practice. For recommended dose modifications based on platelet counts, see section *2.2 Dosage and Administration*.

In pJIA and sJIA patients, platelets should be monitored at the time of the second infusion and thereafter according to good clinical practice (see section *2.2 Dosage and Administration, Dose Modifications*).

Lipid parameters

Elevations of lipid parameters such as total cholesterol, triglycerides and/or low density lipoprotein (LDL) cholesterol have been observed (see section *2.6.1 Undesirable Effects, Clinical Trials*). In the majority of patients, there was no increase in atherogenic indices, and elevations in total cholesterol responded to treatment with lipid lowering agents.

Assessment of lipid parameters should be performed 4 to 8 weeks following initiation of Actemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

Malignancy

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

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, pJIA and sJIA 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’.

Systemic Juvenile Idiopathic Arthritis

Macrophage activation syndrome (MAS)

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

2.4.2 Drug Abuse and Dependence
No studies on the effects on the potential for Actemra to cause dependence have been performed. However, there is no evidence from the available data that Actemra treatment results in dependence.

2.4.3 Ability to Drive and Use Machines
No studies on the effects on the ability to drive and use machine 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.

2.5 Use in Special Populations
2.5.1 Pregnancy
There are no adequate data from the use of Actemra in pregnant women. A study in monkeys did not indicate any dysmorphogenic potential but has yielded a higher number of spontaneous abortion/embryo-fetal death at a high dose (see section *3.3.5 Preclinical Safety, Other*). The relevance of this data for humans is unknown.

Women of childbearing potential must use effective contraception during and up to 6 months after treatment.

Actemra should not be used during pregnancy unless clearly indicated by medical need.

2.5.2 Labour and Delivery
No text.

2.5.3 Nursing Mothers
It is unknown whether Actemra is excreted in human breast milk. Although endogenous immunoglobulins of the IgG isotope are secreted into human milk. 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.

2.5.4 Pediatric Use
(See section *2.2.1 Special Dosage Instructions).*

2.5.5 Geriatric Use
(See sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations).*

2.5.6 Renal Impairment
(See sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations).*

2.5.7 Hepatic Impairment
(See sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations).*

2.6 Undesirable Effects
2.6.1 Clinical Trials
The safety profile in this section comes from 4510 patients exposed to Actemra in clinical trials; the majority of these patients were participating in RA studies (n=4009), while the remaining experience comes from pJIA (n=240), sJIA (n=112) and study in other indication (n=149). The safety profile of tocilizumab across these indications remains similar and undifferentiated.

Adverse Drug Reactions (ADRs) from clinical trials (*Table 1*) are listed by MedDRA system organ class according to clinical importance to the patient. The corresponding frequency category for each ADR is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10) or uncommon (≥ 1/1000 to < 1/100).

Table 1 Summary of ADRs Occurring in RA, pJIA and sJIA Patients Treated with Actemra

MedDRA 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 transaminase increased, Weight increased	Total billirubin increased
Vascular disorders		Hypertension	
Blood and lymphatic system disorders		Leukopenia, Neutropenia	
Metabolism and nutritions disorders		Hypercholesterolaemia	Hypertriglyceridaemia
General disorders and administration site conditions	Injection site reaction	Peripheral edema, Hypersensitivity reaction	
Respiratory, thoracic, and mediastinal disorders		Cough, Dyspnoea	
Eye disorders		Conjunctivities	
Renal disorders			Nephrolithiasis
Endocrine disorders			Hypothyroidsm

Description of selected adverse drug reactions from clinical trials:

Rheumatoid Arthritis

Patient Treated with Actemra IV:
The safety of Actemra IV has been studied in 5 Phase III, double-blind controlled trials and their extension periods.

The *all control* population includes all patients from the double-blind phases of each core study from randomization until either the first change in the treatment regimen, or two years is reached. The control period in 4 of the studies was 6 months and in 1 study was up to 2 years. In the double-blind controlled studies 774 patients received Actemra IV 4 mg/kg in combination with MTX, 1870

patients received Actemra IV 8 mg/kg in combination with MTX/other DMARDs and 288 patients received Actemra IV 8 mg/kg monotherapy.

The *all exposure* population includes all patients who received at least one dose of Actemra IV either in the double-blind control period or open-label extension phase in 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.

Infections
In the 6-month controlled trials, the rate of all infections reported with Actemra IV 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 DMARDs group. In the *all 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 (bacterial, viral and fungal) with Actemra IV 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 Actemra IV group and 1.5 events per 100 patient years of exposure in the MTX group.

In the *all exposure* population the overall rate of serious infections was 4.7 events per 100 patient years. Reported serious infections, some with fatal outcome, included pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have also been reported.

Gastrointestinal Perforation
During the 6-month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient years with Actemra therapy. In the *all exposure* population the overall rate of gastrointestinal perforation was 0.28 events per 100 patient years. Reports of gastrointestinal perforation on Actemra were primarily reported as complications of diverticulitis including generalized purulent peritonitis, lower GI perforation, fistula 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 Actemra IV 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 (occurring in a total of 6/3778 patients) was several-fold higher with the 4 mg/kg arm in comparison to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with Actemra and requiring treatment discontinuation, were reported in a total of 13 out of 3778 patients (0.3%) treated with Actemra during the controlled and open-label clinical trials. These reactions were generally observed during the second to fifth infusions of Actemra (see section *2.4.1 Warnings and Precautions, General*).

Immunogenicity
A total of 2876 patients have been tested for anti-tocilizumab antibodies in the 6-month controlled clinical trials. Forty-six (46) patients (1.6%) developed positive anti-tocilizumab antibodies of

whom 5 had an associated medically significant hypersensitivity reaction leading to withdrawal. Thirty (30) patients (1.1%) developed neutralizing antibodies.

Malignancies
The clinical data are insufficient to assess the potential incidence of malignancy following exposure to Actemra. Long-term safety evaluations are ongoing.

Monotherapy: Actemra IV versus adalimumab
In a 24-week double-blinded, parallel study (monotherapy with Actemra IV 8 mg/kg q4w (n=162) compared to adalimumab 40 mg SC q2w (n=162)), the overall clinical adverse event profile was similar between Actemra IV and adalimumab. The proportion of patients with serious adverse events was balanced between the treatment groups (Actemra IV 11.7% vs. adalimumab 9.9%) with the most common event being infections (3.1% each). 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 Actemra IV compared with adalimumab. Four (2.5%) patients in the Actemra IV 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 Actemra IV 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 Actemra IV arm and 0.19 mmol/L (7 mg/dL) for patients in the adalimumab arm. The safety observed in the Actemra IV arm was consistent with the known safety profile of Actemra IV and no new or unexpected adverse drug reactions were observed (see *Table 1*) (see section *3.1.2 Clinical/Efficacy Studies*).

Patients Treated with Actemra SC:
The safety of Actemra SC in RA was studied in SC-I. The study compared the efficacy and safety of Actemra SC 162 mg administered every week versus Actemra IV 8 mg/kg in 1262 subjects with adult RA. All patients in the study received background non-biologic DMARD(s). The safety and immunogenicity observed for Actemra SC was consistent with the known safety profile of Actemra IV and no new or unexpected adverse drug reactions were observed (see *Table 1*). A higher frequency of injection site reactions was observed in the SC arms compared with placebo SC injections in the IV arms (see section *3.1.2 Clinical/Efficacy Studies*).

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

Immunogenicity
In SC-I, a total of 625 patients treated with Actemra SC 162 mg weekly were tested for anti-tocilizumab antibodies in the 6-month controlled period. Five patients (0.8%) developed positive anti-tocilizumab antibodies; of these, all developed neutralizing anti-tocilizumab antibodies.

A total of 1454 Actemra SC *all exposure* patients have been tested for anti-tocilizumab antibodies, thirteen patients (0.9%) developed positive anti-tocilizumab antibodies, and of these 12 patients (0.8%) developed neutralizing anti-tocilizumab antibodies.

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

Polyarticular Juvenile Idiopathic Arthritis

The safety profile of Actemra was studied in 240 pediatric patients with pJIA. In Study WA19977, 188 patients (2 to 17 years of age) were treated with Actemra IV. The total patient exposure to Actemra in the pJIA *all exposure* population was 184.4 patient years for Actemra IV. In general, the safety profile observed in patients with pJIA was consistent with the known safety profile of Actemra with the exception of ISRs (see *Table 1*).

Infections

Infections are the most commonly observed events in pJIA. The rate of infections in the pJIA Actemra IV *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 below 30 kg treated with 10 mg/kg Actemra IV (12.2 per 100 patient years) compared to patients weighing ≥ 30 kg, treated with 8 mg/kg Actemra IV (4.0 per 100 patient years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing below 30 kg treated with 10 mg/kg Actemra IV (21.4%) compared to patients weighing ≥ 30 kg, treated with 8 mg/kg Actemra IV (7.6%).

Infusion Reactions

In pJIA patients, infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion with Actemra IV. In the Actemra *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 *2.6 Undesirable Effects*).

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

Injection Site Reactions

A total of 28.8% (15/52) pJIA patients experienced ISRs to Actemra SC. These ISRs occurred in 44% of patients ≥ 30 kg compared to 14.8% of patients below 30 kg. The most common ISRs were injection site erythema, swelling, hematoma, pain and pruritis. All ISRs reported were nonserious Grade 1 events, and none of the ISRs required patient withdrawal from treatment or dose interruption.

Immunogenicity

Across the two studies in pJIA patients, a total of four patients (0.5% [1/188] in the IV Study WA19977) developed positive neutralizing anti-tocilizumab antibodies without developing a serious or clinically significant hypersensitivity reaction. Of these 4 patients, 2 subsequently withdrew from the study. No correlation between antibody development and clinical response or adverse events was observed.

Systemic Juvenile Idiopathic Arthritis

The safety profile of tocilizumab in sJIA was studied in 163 pediatric patients. In Study WA18221 (12-week trial and long-term extension), 112 patients (2 to 17 years of age) were treated with Actemra IV and in Study WA28118 (52-week trial), 51 patients (1 to 17 years of age) were treated with Actemra SC. In general, the adverse drug reactions in patients with sJIA were similar in type to those seen in RA patients (see section *2.6 Undesirable Effects*).

Infections
In the 12-week controlled trial (Study WA18221), the rate of all infections in the Actemra IV group was 344.7 per 100 patient years and 287.0 per 100 patient years in the placebo group. In the open-label extension study (Part II) the overall rate of infections remained similar at 306.6 per 100 patient years.

In the 12-week controlled trial (Study WA18221), the rate of serious infections in the Actemra IV group was 11.5 per 100 patient years. In the open-label extension study the overall rate of serious infections remained stable at 11.3 per 100 patient years. Reported serious infections were similar to those seen in RA patients with the addition of varicella and otitis media.

Infusion Reactions
For sJIA patients, infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion with Actemra IV. In the 12-week controlled trial (Study WA18221), four percent (4.0%) of patients from the Actemra 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 trial experience, 16% of patients in the Actemra IV group and 5.4% of patients in the placebo group experienced an event within 24 hours of infusion. In the Actemra group, the events included, but not limited to rash, urticaria, diarrhoea, epigastric discomfort, arthralgia and headache. One of these events (urticaria) was considered serious.

Clinically significant hypersensitivity reactions associated with Actemra IV and requiring treatment discontinuation, were reported in 1 out of 112 patients (below 1%) treated with Actemra IV during the controlled and open-label parts of the clinical trial.

Immunogenicity
In Study WA18221, 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.

2.6.1.1 Laboratory Abnormalities
Haematology abnormalities:

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

Rheumatoid Arthritis
Intravenous Administration:
In the 6-month controlled trials decreases in neutrophil counts below 1 x 10^9/L occurred in 3.4% of patients on Actemra IV 8 mg/kg + DMARD compared to below 0.1% of patients on placebo + DMARD. Approximately half of the instances of ANC below 1 x 10^9/L occurred within 8 weeks of starting therapy. Decreases below 0.5 x 10^9/L were reported in 0.3% patients receiving Actemra IV 8 mg/kg + DMARD (see sections *2.2 Dosage and Administration* and *2.4.1 Warnings and Precautions*).

In the *all control* and *all exposure* population, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 6-month controlled clinical trials.

Subcutaneous Administration:
During routine laboratory monitoring in the Actemra SC 6-month controlled period of clinical trial SC-I, a decrease in neutrophil count below 1×10^9/L occurred in 2.9% of patients on Actemra SC 162 mg weekly.

Polyarticular Juvenile Idiopathic Arthritis
During routine laboratory monitoring in the Actemra IV *all exposure* population, a decrease in neutrophil count below 1×10^9/L occurred in 3.7% of patients treated with Actemra IV.

Systemic Juvenile Idiopathic Arthritis
During routine laboratory monitoring in the 12-week controlled trial (Study WA18221), a decrease in neutrophil counts below 1×10^9/L occurred in 7% of patients in the Actemra IV group, and in none in the placebo group.

In the open-label extension study (WA18221), decreases in neutrophil counts below 1 x 10^9/L, occurred in 15% of Actemra IV group.

Platelets

Rheumatoid Arthritis
Intravenous Administration:
In the 6-month controlled trials decreases in platelet counts below 100 x 10^3/µL occurred in 1.7% of patients on Actemra IV 8 mg/kg plus traditional DMARDs compared to below 1% of patients on placebo plus traditional DMARDs, without associated bleeding events (see sections *2.2 Dosage and Administration* and *2.4.1 Warnings and Precautions*).

In the *all control* and *all exposure* population, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 6-month controlled clinical trials.

Subcutaneous Administration:
During routine laboratory monitoring in the Actemra SC 6-month controlled period of clinical trial SC-I, none of the patients had a decrease in platelet count to $\leq 50 \times 10^3$/µL.

Polyarticular Juvenile Idiopathic Arthritis
During routine laboratory monitoring in the Actemra *all exposure* population, a decrease in platelet count to $\leq 50 \times 10^3$/µL occurred in 1% patients treated with Actemra IV, without associated bleeding events and in no patients treated with Actemra SC.

Systemic Juvenile Idiopathic Arthritis
During routine laboratory monitoring in the 12-week controlled trial (Study WA18221), 3% of patients in the placebo group and 1% in the Actemra IV group had a decrease in platelet count to $\leq 100 \times 10^3$/µL.

In the open-label extension study (WA18221), decreases in platelet counts below 100 x 10^3/µL occurred in 3% of patients of the Actemra IV group, without associated bleeding events.

Liver enzyme elevations

Rheumatoid Arthritis
Intravenous Administration:
During the 6-month controlled trials transient elevations in ALT/AST above 3 x ULN were observed in 2.1% of patients on Actemra IV 8 mg/kg compared to 4.9% of patients on MTX, and in 6.5% of patients who received Actemra IV 8 mg/kg + DMARD compared to 1.5% of patients on placebo + DMARD. The addition of potentially hepatotoxic drugs (e.g. MTX) to Actemra IV monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST above 5 x ULN were observed in 0.7% of Actemra IV monotherapy patients and 1.4% of Actemra IV + DMARD patients, the majority of whom were discontinued from Actemra treatment (see sections *2.2 Dosage and Administration* and *2.4.1 Warnings and Precautions*). During routine laboratory monitoring, the incidence of indirect bilirubin greater than the upper limit of normal was 6.2% in patients treated with 8 mg/kg Actemra IV + DMARD in the *all control* population.
In the *all control* and *all exposure* population, the pattern and incidence of elevations in ALT/AST remained consistent with what was seen in the 6-month controlled clinical trials.

In Study WA25204, of the 1538 patients with moderate to severe RA (see section *3.1.2 Clinical/Efficacy Studies*) and treated with Actemra, elevations in ALT or AST > 3 x ULN occurred in 5.3% and 2.2% patients, respectively. One serious event of drug-induced hepatitis with hyperbilirubinemia was reported in association with Actemra treatment (see section *2.4.1 Warnings and Precautions*)

Subcutaneous Administration:
During routine laboratory monitoring in the Actemra SC 6-month controlled period of clinical trial SC-I, elevation in ALT or AST ≥ 3 x ULN occurred in 6.5% and 1.4% of patients, respectively on SC weekly.

Polyarticular Juvenile Idiopathic Arthritis
During routine laboratory monitoring in the Actemra *all exposure* population, elevation in ALT or AST ≥ 3 x ULN occurred in 3.7% and below 1% of patients treated with Actemra IV.

Systemic Juvenile Idiopathic Arthritis
During routine laboratory monitoring in the 12-week controlled trial (Study WA18221), elevation in ALT or AST ≥ 3 x ULN occurred in 5% and 3% of patients, respectively, in the Actemra IV group, and in 0% of placebo patients.

In the open-label extension study (WA18221), elevation in ALT or AST ≥ 3 x ULN occurred in 12% and 4% of patients, respectively, in the Actemra IV group.

Elevations in lipid parameters

Rheumatoid Arthritis
Intravenous Administration:
During routine laboratory monitoring in the 6-month controlled trials, elevations in lipid parameters (total cholesterol, LDL, HDL, triglycerides) were observed in patients treated with Actemra IV. Approximately 24% of patients receiving Actemra IV in clinical trials experienced sustained elevations in total cholesterol above 6.2 mmol/L (240 mg/dL), with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/L (160 mg/dL).

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

In the *all control* and *all exposure* population, the pattern and incidence of elevations in lipid parameters remained consistent with what was seen in the 6-month controlled clinical trials.

Subcutaneous Administration:
During routine laboratory monitoring in the Actemra SC 6-month controlled period of clinical trial SC-I, 19% of patients on Actemra SC weekly experienced sustained elevations in total cholesterol above 6.2 mmol/L (240 mg/dL), with 9% experiencing a sustained increase in LDL to ≥ 4.1 mmol/L (160 mg/dL) on Actemra SC weekly.

Polyarticular Juvenile Idiopathic Arthritis
During routine laboratory monitoring in the Actemra IV Study WA19977 3.4% and 10.4% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL at any time during the study treatment, respectively.

Systemic Juvenile Idiopathic Arthritis
During routine laboratory monitoring in the 12-week controlled trial (Study WA18221), 13.4% and 33.3% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL, respectively.

In the open-label extension study (WA18221), 13.2% and 27.7% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL, respectively.

2.6.2 Postmarketing Experience

The following adverse drug reactions have been identified from postmarketing experience with tocilizumab (*Table* 2) based on spontaneous case reports, literature cases and cases from non-interventional study programs. Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000).

Table 2 Adverse Drug Reactions from Postmarketing Experience

Adverse Drug Reaction (MedDRA)	Incidence[4]	Frequency Category
Immune system disorders		
Anaphylaxis (fatal)[1, 2]	Not observed in clinical trials	Rare
Skin and subcutaneous tissue disorders		
Stevens-Johnson syndrome[3]	Not observed in clinical trials	Rare
Blood and lymphatic system disorders		
Hypofibrinogenemia	1.3 per 100 patient years	Common
Hepatobiliary disorders		
Drug-induced liver injury	0.027 per 100 patient years	Rare

Hepatitis	0.035 per 100 patient years	Rare
Hepatic failure	0.004 per 100 patient years	Very rare
Jaundice[3]	Not observed in clinical trials	Rare

[1] See section *2.3 Contraindications*
[2] See section *2.4.1 Warnings and Precautions, General*
[3] This adverse reaction was identified through postmarketing surveillance but not observed in clinical trials. The frequency category was estimated as the upper limit of the 95% confidence interval calculated on the basis of the total number of patients exposed to TCZ in clinical trials
[4] Incidence rate calculated based on all-exposure data obtained from relevant completed clinical trials for all indications

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

2.8 Interactions with Other Medicinal Products and Other Forms of Interaction

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

Concomitant administration of a single dose of 10 mg/kg Actemra IV with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure.

Actemra has not been studied in combination with other biological DMARDs.

The expression of hepatic CYP450 enzymes is suppressed by the cytokines, such as IL-6, that stimulate chronic inflammation. Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as Actemra is introduced.

In vitro studies with cultured human hepatocytes demonstrated that IL-6 caused a reduction in CYP1A2, CYP2C9, CYP2C19, and CYP3A4 enzyme expression. Actemra normalizes expression of these enzymes.

The effect of Actemra on CYP enzymes (except CYP2C19 and CYP2D6) is clinically relevant for CYP450 substrates with a narrow therapeutic index, and/or where the dose is individually adjusted.

In a study in RA patients, levels of simvastatin (CYP3A4) were decreased by 57% one week following a single dose of Actemra, to the level similar or slightly higher than those observed in healthy subjects.

When starting or stopping therapy with Actemra, patients taking medicinal products, which are individually dose-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 of these products may need to be adjusted to maintain therapeutic effect. Given its long elimination half-life ($t_{1/2}$), the effect of Actemra on CYP450 enzyme activity may persist for several weeks after stopping therapy.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

In clinical studies with Actemra in RA, rapid decreases in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and serum amyloid A and fibrinogen were observed. Increases in hemoglobin levels were observed, through tocilizumab decreasing the IL-6 driven effects on hepcidin production to increase iron availability.

In healthy subjects administered Actemra 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 Actemra administration (see section *2.4.1 Warnings and Precautions, General)*.

Consistent with the effect on acute phase reactants, treatment with Actemra was associated with reduction in platelet count within the normal range.

In Actemra 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.

3.1.1 Mechanism of Action

Tocilizumab is a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG_1 subclass. Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit sIL-6R and mIL-6R mediated signaling. IL-6 is a multi-functional cytokine, produced by a variety of cell types involved in local paracrine function as well as regulation of systemic physiological and pathological processes such as induction of immunoglobulin secretion, T-cell activation, induction of hepatic acute phase proteins and stimulation of hematopoiesis. IL-6 has been implicated in the pathogenesis of disease including inflammatory diseases, osteoporosis and neoplasia.

The possibility exists for tocilizumab to affect host defences against infections and malignancies. The role of IL-6 receptor inhibition in the development of malignancies is not known.

3.1.2 Clinical/Efficacy Studies

Rheumatoid Arthritis

The efficacy of Actemra IV in alleviating the signs and symptoms of rheumatoid arthritis was assessed in five randomized, double-blind, multicentre studies. Studies I-V required patients ≥ age 18 with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria who had at least 8 tender and 6 swollen joints at baseline.

Actemra IV was administered intravenously every 4 weeks as monotherapy (Study I), in combination with MTX (Studies II, III, V) or with other disease-modifying antirheumatic drugs (DMARDs) (Study IV).

Study I evaluated 673 patients who had not been treated with MTX within 6 months prior to randomization, 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 Actemra IV were given every four weeks as monotherapy. The comparator group

was weekly MTX (dose titrated from 7.5 to a maximum of 20 mg weekly over an 8-week period). The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 24.

Study II, a 2-year study, evaluated 1196 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of Actemra IV or placebo were given every four weeks as blinded therapy for 52 weeks, in combination with stable MTX (10 mg-25 mg weekly). The primary endpoint at Week 24 was the proportion of patients who achieved an ACR20 response criteria. At Week 52 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 of Actemra IV or placebo were given every four weeks, in combination with stable MTX (10 mg-25 mg weekly). Study IV evaluated 1220 patients who had an inadequate response to their existing rheumatologic therapy, including one or more DMARDs. Doses of 8 mg/kg Actemra IV 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 anti-TNF therapies. The anti-TNF agent was discontinued prior to randomization. Doses of 4 or 8 mg/kg of Actemra IV or placebo were given every four weeks, in combination with stable MTX (10 mg-25 mg weekly). The primary endpoint for studies III-V was the proportion of patients who achieved an ACR20 response at Week 24.

The percent of patients achieving ACR20, 50 and 70 responses in Studies I to V are shown in Table 3.

The efficacy of Actemra SC was assessed in a double-blind, controlled, multicentre study in patients with active RA. The study (SC-I) required patients to be above 18 years of age with active rheumatoid arthritis diagnosed according to ACR criteria and who had at least 4 tender and 4 swollen joints at baseline. All patients received background non-biologic DMARD(s).

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

Table 3 ACR Responses in MTX/Placebo-Controlled Trials (Percent of Patients)

	Study I AMBITION		**Study II LITHE**		**Study III OPTION**		**Study IV TOWARD**		**Study V RADIATE**	
Response Rate	**TCZ 8 mg/kg** **n=286**	**MTX** **n=284**	**TCZ 8 mg/kg + MTX** **n=398**	**PBO + MTX** **n=393**	**TCZ 8 mg/kg + MTX** **n=205**	**PBO + MTX** **n=204**	**TCZ 8 mg/kg + DMARD** **n=803**	**PBO + DMARD** **n=413**	**TCZ 8 mg/kg + MTX** **n=170**	**PBO + MTX** **n=158**
ACR20										
Week 24	70%***	52%	56%***	27%	59%***	26%	61%***	24%	50%***	10%
Week 52			56%***	25%						
ACR 50										
Week 24	44%**	33%	32%***	10%	44%***	11%	38%***	9%	29%***	4%
Week 52			36%***	10%						

ACR 70										
Week 24	28%**	15%	13%***	2%	22%***	2%	21%***	3%	12%**	1%
Week 52			20%***	4%						
MCR † by Week 52			7%	1%						

TCZ - Actemra IV
MTX - Methotrexate
PBO - Placebo
DMARD - Disease modifying antirheumatic 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*
† MCR = major clinical response, defined as an ACR70 response maintained for any 24 consecutive weeks or more

In all studies, 8 mg/kg Actemra IV-treated patients had statistically significant higher ACR20, 50, 70 response rates at 6 months compared to control. 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 the 8 mg/kg Actemra IV-treated patients significant improvements were noted on all individual components of the ACR response (tender and swollen joint counts), patients and physician global assessment, disability index scores (HAQ), pain assessment and CRP compared to patients receiving placebo + MTX/DMARDs in all studies.

Actemra IV 8 mg/kg treated patients had a statistically significantly greater reduction in disease activity score (DAS28) than patients treated with placebo + DMARD. A good to moderate EULAR response was achieved by significantly more Actemra IV-treated patients compared to patients treated with placebo + DMARD (*Table 4*).

Table 4 Cross-Study Comparison of DAS and EULAR Responses at Week 24

	Study I AMBITION MTX Naive		**Study II LITHE Inadequate Response to MTX**		**Study III OPTION Inadequate Response to MTX**		**Study IV TOWARD Inadequate Response to DMARD**		**Study V RADIATE Inadequate Response to TNF Blocking Agent**	
	TCZ 8 mg/kg n=286	**MTX n=284**	**TCZ 8 mg/kg + MTX n= 398**	**Placebo + MTX n=393**	**TCZ 8 mg/kg + MTX n= 205**	**Placebo + MTX n=204**	**TCZ 8 mg/kg + DMARD n=803**	**Placebo + DMARD n=413**	**TCZ 8 mg/kg + MTX n=170**	**Placebo + MTX n=158**
Change in DAS28 [mean (Adjusted mean (SE))]										
Week 24	-3.31 (0.12)	-2.05 (0.12)	-3.11 (0.09)***	-1.45 (0.11)	-3.43 (0.12)***	-1.55 (0.15)	-3.17 (0.07)***	-1.16 (0.09)	-3.16 (0.14) ***	-0.95 (0.22)
DAS < 2.6 response (%)										
Week 24	33.6%	12.1%	≠33.3%***	3.8%	27.5%***	0.8%	30.2%***	3.4%	30.1% ***	1.6%
EULAR response (%)										
None	18%	35%	26%	65%	20%	65%	20%	62%	32%	84%
Moderate	42%	48%	34%	29%	41%	32%	40%	33%	31%	15%
Good†	40%	17%	41%***	6%	38%***	3%	40%***	4%	37%***	2%

TCZ = Actemra IV
†The p-value compares across all the EULAR categories
** p < 0.05, tocilizumab vs. placebo + MTX/DMARD*
*** p < 0.01, tocilizumab vs. placebo + MTX/DMARD*
**** p < 0.0001, tocilizumab vs. placebo + MTX/DMARD*
≠ In study II, 47% of patients achieved a DAS28 < 2.6 at 52 weeks compared to 33% of patients at Week 24

Table 5 Clinical Response at Week 24 in Actemra SC Trial (Percent of Patients)

	SC-I[a]	
	Actemra SC 162 mg every week + DMARD(s) n=558	**Actemra IV 8 mg/kg + DMARD(s) n=537**
ACR20		
Week 24	69.4%	73.4%
Weighted difference (95% CI)	-4.0 (-9.2, 1.2)	
ACR50		
Week 24	47.0%	48.6%
Weighted difference (95% CI)	-1.8 (-7.5, 4.0)	
ACR70		
Week 24	24.0%	27.9%
Weighted difference (95% CI)	-3.8 (-9.0, 1.3)	
Change in DAS28 [adjusted mean]		
Week 24	-3.5	-3.5
Adjusted mean difference (95% CI)	0 (-0.2, 0.1)	
DAS28 < 2.6		
Week 24	38.4%	36.9%
Weighted difference (95% CI)	0.9 (-5.0, 6.8)	
EULAR response (%)		
None	3.3%	4.8%
Moderate	41.7%	42.7%
Good	55.0%	52.4%

a=Per Protocol Population

Major Clinical Response

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

Radiographic Response – Intravenous Administration

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 Actemra compared to control.

In the open-label extension of Study II the inhibition of progression of structural damage in Actemra/MTX-treated patients was maintained in the second year of treatment.

Table 6 Radiographic Mean Changes at 52 Weeks and 104 Weeks in Study II

	PBO + MTX (+ option of TCZ from Week 16)	**TCZ 8 mg/kg + MTX**
Changes from baseline to Week 52		
n	294	353
Total Sharp-Genant score	1.17	0.25
Erosion score	0.76	0.15
JSN score	0.41	0.10
Change from Week 52 to Week 104		
n	294	353
Total Sharp-Genant score	0.79	0.12
Erosion score	0.48	0.07
JSN score	0.31	0.05

PBO - Placebo
MTX - Methotrexate
TCZ - Actemra IV
JSN - Joint space narrowing
All data presented was read together in campaign 2 which consists of the evaluations of the baseline, Week 24, Week 52, Week 80, Week 104 and early withdrawal or escape therapy readings taken up to Week 104 visit

Following 1 year of treatment with Actemra/MTX, 83% of patients had no progression of structural damage, as defined by a change in the TSS score of zero or less, compared with 67% of placebo/MTX-treated patients. This remained consistent following 2 years of treatment (83%). Ninety three percent (93%) of patients had no progression between Week 52 and Week 104.

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.

Radiographic Response – Subcutaneous Administration

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

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

Quality of Life Outcomes – Intravenous Administration

Clinically significant improvements in disability index (HAQ-DI, Health Assessment Questionnaire Disability Index), fatigue (FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy Fatigue) and improvement in both the physical (PCS, Physical Component Summary) and mental health (MCS, Mental Component Summary) domain of the SF-36 (Short Form 36) were observed in patients treated with 8 mg/kg Actemra (monotherapy or combination with DMARDs) compared to patients treated with MTX/DMARDs (Table 7).

At Week 24, the proportion of Actemra IV 8 mg/kg treated patients showing a clinically relevant improvement in HAQ-DI (defined as an individual total score decrease of above 0.25), was significantly higher than among patients receiving placebo + MTX/DMARDs in all studies. During the open-label period of Study II the improvement in physical function has been maintained for up to 2 years.

Table 7 Comparison of SF-36, HAQ and FACIT-Fatigue Responses at Week 24

Study I AMBITION MTX-Naïve		**Study II LITHE** Inadequate Response to MTX		**Study III OPTION** Inadequate Response to MTX		**Study IV TOWARD** Inadequate Response to DMARD		**Study V RADIATE** Inadequate Response to TNF Blocking Agent	
TCZ 8 mg/kg **n=286**	**MTX** **n=284**	**TCZ 8 mg/kg + MTX** **n= 398**	**Placebo + MTX** **n=393**	**TCZ 8 mg/kg + MTX** **n=205**	**Placebo + MTX** **n=204**	**TCZ 8 mg/kg + DMARD** **n=803**	**Placebo + DMARD** **n=413**	**TCZ 8 mg/kg + MTX** **n=170**	**Placebo + MTX** **n=158**
Change in PCS [mean (Adjusted mean (SE))]									
10.2 (0.7)	8.4 (0.7)	8.1 (0.6)**	5.6 (0.7)	9.5 (0.8)***	5.0 (1.0)	8.9 (0.4)***	4.1 (0.6)	8.0 (0.9)**	2.2 (1.3)
Change in MCS [mean (Adjusted mean (SE))]									
6.7 (0.9)	5.0 (0.9)	4.2 (0.8)	2.8 (0.9)	7.3 (1.1)**	2.7 (1.3)	5.3 (0.6)**	2.3 (0.7)	4.1 (1.3)	4.1 (1.9)
Change in HAQ-DI [mean (Adjusted mean (SE))]									
-0.70 (0.05)	-0.52 (0.05)	-0.5 (0.04)**	-0.3 (0.04)	-0.55 (0.06)**	-0.34 (0.07)	-0.47 (0.03)***	-0.2 (0.03)	-0.39 (0.05)***	-0.05 (0.07)
Change in FACIT-Fatigue [mean (Adjusted mean (SE))]									
9.3 (0.8)	7.0 (0.8)	6.4 (0.7)	5.4 (0.8)	8.6 (0.9)***	4.0 (1.0)	8.0 (0.5)***	3.6 (0.7)	8.8 (1.0)*	4.2 (1.6)

TCZ = Actemra IV
** p < 0.05, tocilizumab vs. placebo + MTX/DMARD*
*** p < 0.01, tocilizumab vs. placebo + MTX/DMARD*
**** p < 0.0001, tocilizumab vs. placebo + MTX/DMARD*

In study II, changes in PCS, MCS and FACIT-Fatigue at 52 weeks were 10.1***, 5.4 and 8.4**, respectively, in the Actemra IV 8 mg/kg + MTX group compared to 5.6, 3.8 and 5.5, respectively, in the placebo plus MTX group. At Week 52, the mean change in HAQ-DI was -0.58 in the Actemra IV 8 mg/kg + MTX group compared with -0.39 in the placebo + MTX group. The mean change in HAQ-DI was maintained at Week 104 in the Actemra IV 8 mg/kg + MTX group (-0.61).

Quality of Life Outcomes – Subcutaneous Administration

In study SC-I, the mean decrease in HAQ-DI from baseline to Week 24 was 0.6 for both Actemra SC 162 mg weekly and Actemra IV 8 mg/kg every 4 weeks. The proportion of patients achieving a clinically relevant improvement in HAQ-DI at Week 24 (change from baseline of ≥ 0.3 units) was comparable in the Actemra SC every week group (65.2%) versus the Actemra IV 8 mg/kg group (67.4%), with a weighted difference in proportions of -2.3% (95% CI -8.1, 3.4). The SF-36 summary was split into mental and physical components. The mental component scores were similar between the groups, with a mean change from baseline at Week 24 of 6.22 for the SC group and 6.54 for the IV group. The physical component scores were also similar between the groups, with mean change from baseline at Week 24 of 9.49 for the SC group and 9.65 for the IV group.

Laboratory Evaluations

Treatment with Actemra IV 8 mg/kg in combination with DMARD/MTX or as monotherapy resulted in a highly statistically significant improvement in haemoglobin levels compared with placebo + MTX/DMARD ($p < 0.0001$) at Week 24. The greatest improvement was observed in patients with chronic anaemia associated with RA; mean haemoglobin levels increased by Week 2 and remained within normal range through Week 24.

A marked decrease in mean levels of acute phase reactants, CRP, ESR, and serum amyloid A occurred rapidly after Actemra administration. Consistent with the effect on acute phase reactants, treatment with Actemra was associated with reduction in platelet count within the normal range.

Monotherapy: Actemra versus adalimumab

Study WA19924 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 Actemra arm received an Actemra IV (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 Actemra 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 8*).

Table 8 Efficacy Results for Study 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 (%)	18 (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

Cardiovascular Outcomes

Study WA25204 was a randomized, open-label (sponsor-blinded), 2-arm parallel group, multicenter, non-inferiority, cardiovascular (CV) outcomes trial in patients with a diagnosis of moderate to severe RA. This CV safety study was designed to exclude a moderate increase in CV risk in patients treated with Actemra compared with a TNF inhibitor standard of care (etanercept [ETA]).

The study included 3080 seropositive RA patients with active disease and an inadequate response to non-biologic disease-modifying antirheumatic drugs, who were aged ≥ 50 years with at least one additional CV risk factor beyond RA. Patients were randomized 1:1 to Actemra IV 8 mg/kg Q4W or SC ETA 50 mg QW and followed for an average of 3.2 years. The primary endpoint was the comparison of the time-to-first occurrence of any component of a composite of major adverse CV events (MACE; non-fatal myocardial infarction, non-fatal stroke, or CV death), with the final intent-to-treat analysis based on a total of 161 confirmed CV events reviewed by an independent and blinded adjudication committee.

Non-inferiority of Actemra to ETA for cardiovascular risk was determined by excluding a > 80% relative increase in the risk of MACE. The primary endpoint was met such that a > 43% increase in the risk of MACE could be excluded (hazard ratio [HR] comparing Actemra to ETA=1.05; 95% CI=0.77, 1.43).

Polyarticular Juvenile Idiopathic Arthritis

The efficacy of Actemra IV was assessed in a three-part study including an open-label extension in children with active polyarticular juvenile idiopathic arthritis (pJIA). Part I consisted of a 16-week active Actemra IV treatment lead in period (n=188) followed by Part II, a 24-week randomized double-blind placebo-controlled withdrawal period (ITT, n=163), followed by Part III, a 64-week open-label period. Eligible patients ≥ 30 kg received Actemra IV at 8 mg/kg for 4 doses. Patients below 30 kg were randomized 1:1 to receive either Actemra IV 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 entered the blinded withdrawal period (Part II) of the

study. In Part II, patients were randomized to Actemra IV (same dose received in Part I) or placebo in a 1:1 ratio was stratified by concurrent methotrexate 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.

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 Actemra-treated patients. These proportions were statistically significantly different (p=0.0024).

At the conclusion of Part I, JIA ACR30/50/70/90 responses were 89.4%, 83.0%, 62.2%, and 26.1%, respectively.

During the withdrawal phase (Part II), the percent of patients achieving JIA ACR30, 50, and 70 responses at Week 40 relative to baseline are shown in the table below.

Table 9 JIA ACR Response Rates at Week 40 Relative to Baseline (Percent of Patients)

Response Rate	TCZ n=82	Placebo n=81
JIA ACR30	74.4%†	54.3%†
JIA ACR50	73.2%†	51.9%†
JIA ACR70	64.6%†	42.0%†

† *p < 0.01, Actemra IV vs. placebo*

Systemic Juvenile Idiopathic Arthritis

The efficacy of Actemra IV for the treatment of active sJIA was assessed in a 12-week randomized, double-blind, placebo-controlled, parallel group, 2-arm study. Patients (treated with or without MTX) were randomized (TCZ: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 below 30 kg and 37 patients were assigned to receiving placebo infusions every two weeks. Corticosteroid tapering could occur from Week 6 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 extension phase at weight appropriate dosing.

The primary endpoint was the proportion of patients with at least 30% improvement in 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 the patients treated with TCZ and 24.3% (9/37) of placebo patients achieved this endpoint. These proportions were highly significantly different (p < 0.0001).

The percent of patients achieving JIA ACR30, 50, 70 and 90 responses are shown in the table below. Responses are maintained in the open-label extension.

Table 10 JIA ACR Response Rates at Week 12 (Percent of Patients)

Response Rate	TCZ n=75	Placebo n=37
ACR30	90.7%*	24.3%
ACR50	85.3%*	10.8%
ACR70	70.7%*	8.1%

ACR90	37.3%*	5.4%

** p < 0.0001, Actemra IV vs. placebo*

Systemic Features

In those patients treated with tocilizumab, 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 only 21% of placebo patients (p < 0.0001) and 64% of tocilizumab-treated patients with rash characteristic of sJIA at baseline were free of rash at Week 12 versus 11% of placebo patients (p=0.0008).

There was a highly statistically significant reduction in pain for tocilizumab-treated patients at Week 12 in comparison to placebo patients. 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).

The responses for systemic features are maintained in the open-label extension.

Corticosteroid Tapering

Of the 31 placebo and 70 tocilizumab patients receiving oral corticosteroids at baseline, 8 placebo and 48 tocilizumab patients achieved a JIA ACR70 response at Week 6 or 8 enabling corticosteroid dose reduction. Seventeen (24%) tocilizumab patients versus 1 (3%) placebo patient were able to reduce the 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 ACR responses.

Quality of Life

At Week 12, the proportion of tocilizumab-treated patients showing a minimally clinically important improvement in CHAQ-DI (defined as an individual total score decrease of ≥ 0.13) was significantly higher than in patients receiving placebo, 77% versus 19% (p < 0.0001). Responses are maintained in the open-label extension.

Laboratory Parameters

Fifty out of seventy five (67%) patients treated with tocilizumab had a haemoglobin below LLN at baseline. Forty (80%) of these patients with decreased haemoglobin had an increase in their haemoglobin to within the normal range at Week 12, in comparison to only 2 out of 29 (7%) of placebo patients with haemoglobin below LLN at baseline (p < 0.0001). Forty four (88%) tocilizumab patients with decreased haemoglobin at baseline had an increase in their haemoglobin by ≥ 10 g/L at Week 6 versus 1 (3%) placebo patient (p < 0.0001).

The proportion of tocilizumab-treated patients with thrombocytosis at baseline who had a normal platelet count at Week 12 was significantly higher than in the placebo patients, 90% versus 4% (p < 0.0001).

A marked decrease in mean levels of acute phase reactants, CRP, ESR, and serum amyloid A occurred rapidly after tocilizumab administration.

3.2 Pharmacokinetic Properties

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

Rheumatoid Arthritis
Intravenous Administration:

The pharmacokinetics of Actemra IV were determined using a population pharmacokinetic analysis on a database composed of 1793 RA patients treated with a one-hour infusion of 4 and 8 mg/kg Actemra IV every 4 weeks for 24 weeks.

The pharmacokinetic parameters of Actemra IV did not change with time. A more than dose-proportional increase in area under the curve (AUC) and trough concentration (C_{min}) was observed for doses of 4 and 8 mg/kg every 4 weeks. Maximum concentration (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.

The following parameters (predicted mean ± SD) were estimated for a dose of Actemra IV 8 mg/kg 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}) = 183 ± 85.6 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} (2.47), which was expected based on the nonlinear 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. Actemra IV 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 Actemra IV 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.

Population PK analysis identified body weight as a significant covariate impacting pharmacokinetics of Actemra. When given IV on a mg/kg basis, individuals with body weight ≥ 100 kg are predicted to have mean steady-state exposures higher than mean values for the patient population. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended in patients ≥ 100 kg (see section *2.2 Dosage and Administration*).

The following parameters are valid for a dose of Actemra IV 4 mg/kg given every 4 weeks. Predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 12000 ± 4000 mcg•h/mL, 17.8 ± 6.1 mcg/mL, and 83.8 ± 23.1 mcg/mL, respectively. The accumulation ratios for AUC and C_{max} were small; 1.09 and 1.01, respectively. The accumulation ratio was higher for C_{min} (2.62). Steady-state was reached following the first administration for C_{max} and AUC, respectively, and after 16 weeks for C_{min}.

Subcutaneous Administration:

The pharmacokinetics of Actemra SC were determined using a population pharmacokinetic analysis on a database composed of 1759 rheumatoid arthritis patients treated with Actemra SC 162 mg every week, Actemra SC 162 mg every other week, and Actemra IV 8 mg/kg every 4 weeks for 24 weeks.

The pharmacokinetic parameters of Actemra SC did not change with time. For the Actemra SC 162 mg every week dose, the predicted mean (±SD) steady-state AUC_{1week}, C_{min} and C_{max} of tocilizumab were 8200 ± 3600 mcg•h/mL, 44.6 ± 20.6 mcg/mL, and 50.9 ± 21.8 mcg/mL, respectively. The accumulation ratios for AUC, C_{min}, and C_{max} were 6.83, 6.37, and 5.47, respectively. Steady-state was reached after 12 weeks for AUC, C_{min}, and C_{max}.

For the Actemra SC 162 mg every other week dose, the predicted mean (±SD) steady-state AUC_{2week}, C_{min}, and C_{max} of Actemra SC were 3200 ± 2700 mcg•h/mL, 5.6 ± 7.0 mcg/mL, and 12.3 ± 8.7 mcg/mL, respectively. The accumulation ratios for AUC, C_{min}, and C_{max} were 2.67, 5.6, and 2.12, respectively. Steady-state was reached after 12 weeks for AUC and C_{min}, and after 10 weeks for C_{max}.

Polyarticular Juvenile Idiopathic Arthritis

The pharmacokinetics of Actemra in pJIA patients was characterized by a population pharmacokinetic analysis which included 237 patients who were treated with Actemra IV 8 mg/kg every 4 weeks (patients weighing ≥ 30 kg), Actemra IV 10 mg/kg every 4 weeks (patients weighing below 30 kg).

Table 11 Predicted Mean ± SD PK Parameters at Steady-State After IV Dosing in pJIA

	IV	
TCZ PK Parameter	**8 mg/kg Q4W ≥ 30 kg**	**10 mg/kg Q4W below 30 kg**
C_{max} (µg/mL)	183 ± 42.3	168 ± 24.8
C_{trough} (µg/mL)	6.55 ± 7.93	1.47 ± 2.44
C_{mean} (µg/mL)	42.2 ± 13.4	31.6 ± 7.84
Accumulation C_{max}	1.04	1.01
Accumulation C_{trough}	2.22	1.43
Accumulation C_{mean} or AUC_{τ} *	1.16	1.05

*τ = 4 weeks for IV regimens

After Actemra IV dosing, approximately 90% of the steady-state was reached by Week 12 for the 10 mg/kg (BW < 30 kg), and by Week 16 for the 8 mg/kg (BW ≥ 30 kg) dose.

Systemic Juvenile Idiopathic Arthritis

The pharmacokinetics of Actemra in sJIA patients was characterized by a population pharmacokinetic analysis which included 140 patients who were treated with 8 mg/kg IV every 2 weeks (patients weighing ≥ 30 kg), 12 mg/kg IV every 2 weeks (patients weighing below 30 kg).

Table 12 Predicted Mean ± SD PK Parameters at Steady-State After IV Dosing in sJIA

	IV	
TCZ PK Parameter	**8 mg/kg Q2W ≥ 30 kg**	**12 mg/kg Q2W below 30 kg**
C_{max} (µg/mL)	256 ± 60.8	274 ± 63.8
C_{trough} (µg/mL)	69.7 ± 29.1	68.4 ± 30.0
C_{mean} (µg/mL)	119 ± 36.0	123 ± 36.0
Accumulation C_{max}	1.42	1.37
Accumulation C_{trough}	3.20	3.41
Accumulation C_{mean} or AUC_{τ} *	2.01	1.95

*τ = 2 weeks for IV regimens

After Actemra IV dosing, approximately 90% of the steady-state was reached by Week 8 for both the 12 mg/kg and 8 mg/kg Q2W regimens.

3.2.1 Absorption

Following Actemra SC dosing in rheumatoid arthritis patients, the absorption half-life was around 4 days. The bioavailability for the SC formulation was 0.8.

3.2.2 Distribution

Following Actemra IV dosing, Actemra undergoes biphasic elimination from the circulation. In rheumatoid arthriris 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.

In pediatric patients with pJIA, the central volume of distribution was 1.98 L, the peripheral volume of distribution was 2.1 L, resulting in a volume of distribution at steady-state of 4.08 L.

In pediatric patients with sJIA, the central volume of distribution was 1.87 L, the peripheral volume of distribution was 2.14 L resulting in a volume of distribution at steady-state of 4.01 L.

3.2.3 Metabolism

No text.

3.2.4 Elimination

The total clearance of Actemra was concentration-dependent and is the sum of the linear and nonlinear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 12.5 mL/h in rheumatoid arthritis patients and 5.8 mL/h in pediatric patients with pJIA and 5.7 mL/h in pediatric patients with sJIA. The concentration-dependent nonlinear clearance plays a major role at low Actemra concentrations. Once the nonlinear clearance pathway is saturated, at higher Actemra concentrations, clearance is mainly determined by the linear clearance.

In RA patients, for intravenous administration, the $t_{1/2}$ of Actemra IV was concentration-dependent in rheumatoid arthritis, the concentration-dependent apparent $t_{1/2}$ is up to 11 days for 4 mg/kg and 13 days for 8 mg/kg every 4 weeks in patients with RA at steady-state. For subcutaneous administration, the concentration-dependent apparent $t_{1/2}$ is up to 13 days for Actemra SC 162 mg every week and 5 days for Actemra SC 162 mg every other week in patients with RA at steady-state. At high serum concentrations, when total clearance of Actemra SC is dominated by linear

clearance, a terminal $t_{1/2}$ of approximately 21.5 days was derived from the population parameter estimates.

In children with pJIA, the effective $t_{1/2}$ of Actemra IV is up to 17 days for the two body weight categories (8 mg/kg for body weight ≥ 30 kg or 10 mg/kg for body weight below 30 kg) during a dosing interval at steady-state.

In children with sJIA, the effective $t_{1/2}$ of Actemra IV is up to 16 days for both the 12 mg/kg and 8 mg/kg Q2W regimens during a dosing interval at steady-state.

3.2.5 Pharmacokinetics in Special Populations

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

Renal impairment: No formal study of the effect of renal impairment on the pharmacokinetics of Actemra has been conducted.

Most of the patients in the RA studies population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (estimated creatinine clearance based on Cockcroft-Gault formula) did not impact the pharmacokinetics of Actemra. No dose adjustment is required in patients with mild renal impairment.

Other populations: Population pharmacokinetic analyses in adult RA patients, showed that age, gender and ethnic origin did not affect the pharmacokinetics of Actemra. No dose adjustment is necessary for these demographic factors.

3.3 Nonclinical Safety Data

3.3.1 Carcinogenicity

A carcinogenicity study of tocilizumab has not been conducted. Available preclinical data, showed the contribution of the pleiotropic cytokine IL-6 to malignant progression and apoptosis resistance to various cancer types. These data do not suggest a relevant risk for cancer initiation and progression under therapy with tocilizumab. Accordingly, proliferate lesions have not been observed in a chronic cynomolgus monkey 6-month toxicity study nor were they described in IL-6 knock-out mice under chronic IL-6 depletion.

3.3.2 Genotoxicity

Standard genotoxicity studies with Actemra in both prokaryotic and eukaryotic cells were all negative.

3.3.3 Impairment of Fertility

Nonclinical data do not suggest an effect on fertility under treatment with analogue of Actemra. Effects on endocrine active organs or on organs of reproductive system were not seen in a chronic cynomolgus monkey toxicity study, nor was the reproductive performance affected in IL-6 deficient male and female mice.

3.3.4 Reproductive Toxicity

When Actemra was administered intravenously to cynomolgus monkeys during early gestation, no direct or indirect harmful effects on pregnancy or embryonal-fetal development were observed.

3.3.5 Other

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

In an embryo-fetal toxicity study conducted in cynomolgus monkeys a slight increase of abortion/embryonal-fetal death was observed with high systemic cumulative exposure (above 100 times human exposure) in the 50 mg/kg/day high-dose group compared to placebo and other low-dose groups. The abortion incidence was within the historical background for the cynomolgus monkey in captivity and the individual cases of abortions/embryo-fetal death did not show any consistent relationship to dosing or duration of dosing with Actemra. Although IL-6 does not seem to be a critical cytokine for either fetal growth or the immunological control of the maternal/fetal interface, a relation of this finding to tocilizumab cannot be excluded.

Transfer of a murine analogue of Actemra into the milk of lactating mice has been observed.

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

The nonclinical safety profile of Actemra in the cynomolgus monkey does not suggest a difference between IV and SC routes of administration.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

Actemra IV:

This medicine should not be used after the expiry date (EXP) shown on the pack.

For vials: Store between 2ºC-8ºC, do not freeze. Keep the container in the outer carton in order to protect from light.

For prepared infusion solution: The prepared solution of Actemra is physically and chemically stable in sodium chloride 9 mg/mL (0.9%) solution for injection. It can be stored for 24 hours at 30ºC and up to 2 weeks in a refrigerator at 2ºC-8°C.

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 should not be longer than 24 hours at 2°C–8°C, unless dilution has taken place in controlled and validated aseptic conditions.

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

Actemra SC:

The medicine should not be used after the expiry date shown on the PFS and the pack. Store the PFS in a refrigerator at a temperature of 2°C–8°C. Do not freeze, keep in carton to protect from light, and keep dry.

Once removed from the refrigerator, the PFS can be stored up to 2 weeks at or below 30^0 C. The PFS must be kept in the carton to protect from light and keep dry.

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in the list excipients.

4.2 Special Instructions for Use, Handling and Disposal

Actemra IV:

Instructions for dilution prior to administration

Parenteral medications 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 must be infused.

Use a sterile needle and syringe to prepare Actemra IV.

Rheumatoid Arthritis:

From a 100 mL infusion bag, withdraw a volume of 0.9% sodium chloride solution, equal to the volume of Actemra solution required for the patient's dose. Withdraw the required amount of Actemra (0.4 mL/kg) under aseptic conditions and dilute to a calculated Actemra concentration in a 100 mL infusion bag containing sterile, nonpyrogenic 0.9% sodium chloride solution. To mix the solution, gently invert the bag to avoid foaming.

pJIA and sJIA patients ≥ 30 kg:

From a 100 mL infusion bag, withdraw a volume of 0.9% sodium chloride solution equal to the volume of the Actemra solution required for the patient's dose. Withdraw the required amount of Actemra (0.4 mL/kg) under aseptic conditions and dilute to a calculated Actemra concentration in a 100 mL infusion bag containing sterile, nonpyrogenic 0.9% sodium chloride solution. To mix the solution, gently invert the bag to avoid foaming.

pJIA patients below 30 kg:

From a 50 mL infusion bag, withdraw a volume of 0.9% sodium chloride solution equal to 0.5 mL/kg of the patient's body weight and discard. This volume should be replaced in the saline bag with an equal volume of Actemra under aseptic conditions. To mix the solution, gently invert the bag to avoid foaming.

sJIA patients below 30 kg:

From a 50 mL infusion bag, withdraw a volume of 0.9% sodium chloride solution equal to 0.6 mL/kg of the patient's body weight and discard. This volume should be replaced in the saline bag with an equal volume of Actemra under aseptic conditions. To mix the solution, gently invert the bag to avoid foaming.

Actemra SC:

Do not use if the medicine is cloudy or contains particles, is any colour besides colourless to yellowish, or any part of the PFS + NSD appears to be damaged.

Disposal of syringes/sharps

The following points should be strictly adhered to regarding the use and disposal of the PFS + NSD:

- Syringes should never be reused.
- Place all used syringes into a sharps container (puncture-proof disposable container).
- Keep this container out of the reach of children.
- Placing used sharps containers in the household waste should be avoided.
- Dispose of the full container according to local requirements or as instructed by your healthcare provider.

For home use, patients should procure a puncture resistant container for the disposal of used syringes.

Actemra is for single-use only.

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

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater, and disposal through household waste should be avoided. Use established "*collection systems"* if available in your location.

Packs
Actemra IV:

Box, 1 vial @ 4 mL (80 mg)	Reg.No.: DKI2157509549A1
Box, 1 vial @ 10 mL (200 mg)	Reg.No.: DKI2157509549A1
Box, 1 vial @ 20 mL (400 mg)	Reg.No.: DKI2157509549A1

Actemra SC:

Box, 4 prefilled syringes @ 0.9 mL (162 mg)	Reg.No.: DKI2157509643A1

Medicine: keep out of reach and sight of children Obat: Jauhkan dari jangkauan dan pandangan anak-anak **On medical prescription only** **Harus dengan resep dokter**
Pada proses pembuatannya bersinggungan dengan bahan bersumber babi.

Made by:
Actemra IV:
Chugai Pharma Manufacturing Co, Ltd., Utsunomiya-City, Japan

Actemra SC:
Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany

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

Imported by:
PT Menarini Indria Laboratories, Bekasi, Indonesia

Distributed by:
PT Roche Indonesia, Jakarta, Indonesia

This PI draft has been reviewed and approved for submission by Rahmawati on 14-Aug-2023