ACTEMRA® 162mg SC

TOCILIZUMAB

Solution for injection in pre-filled syringe

1. NAME OF THE MEDICINAL PRODUCT

Actemra 162 mg S.C. solution for injection in pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

A colourless to slightly yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, Actemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Actemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

Actemra is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Actemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Actemra in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Actemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

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

Actemra (tocilizumab) is indicated for the treatment of giant cell arteritis (GCA) in adult patients.

4.2 Posology and method of administration

Tocilizumab SC formulation is administered with a single-use PFS+NSD. Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA, sJIA, pJIA and / or GCA. The first injection should be performed under the supervision of a qualified health care professional. A patient or parent/guardian can self-inject Actemra only if the physician determines that it is appropriate and the patient or parent/guardian agrees to medical follow-up as necessary and has been trained in proper injection technique.

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

Suitability of the patient or parent/guardian for subcutaneous home use should be assessed and patients or parent/guardian instructed to inform a healthcare professional before administering the next dose if they experience symptoms of an allergic reaction. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions (see section 4.4).

Posology

RA
The recommended posology is subcutaneous 162 mg once every week.

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

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

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

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

RA and GCA

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

- Liver enzyme abnormalities

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

- Low absolute neutrophil count (ANC)

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

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

- Low platelet count

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

RA and GCA

Missed dose

If a patient misses a subcutaneous weekly injection of Actemra within 7 days of the scheduled dose, he/she should be instructed to take the missed dose on the next scheduled day. If a patient misses a

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

Special populations

Elderly:
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. Actemra has not been studied in patients with moderate to severe renal impairment (see section 5.2). Renal function should be monitored closely in these patients.

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

Paediatric patients
The safety and efficacy of Actemra subcutaneous formulation in children from birth to less than 1 year have not been established. No data are available.

A change in dose should only be based on a consistent change in the patient's body weight over time. Actemra can be used alone or in combination with MTX.

sJIA Patients
The recommended posology in patients above 1 year of age is subcutaneous 162 mg once every week in patients weighing greater than or equal to 30 kg or subcutaneous 162 mg once every 2 weeks in patients weighing less than 30 kg.
Patients must have a minimum body weight of 10 kg when receiving Actemra subcutaneously.

pJIA Patients:
The recommended posology in patients above 2 years of age is subcutaneous 162 mg once every 2 weeks in patients weighing greater than or equal to 30 kg or subcutaneous 162 mg once every 3 weeks in patients weighing less than 30 kg.

Dose adjustments due to laboratory abnormalities (sJIA and pJIA)

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

- Liver enzyme abnormalities

Laboratory Value	**Action**
> 1 to 3 x ULN	Modify the dose of the concomitant MTX if appropriate For persistent increases in this range, interrupt Actemra until ALT/AST have normalized.
> 3 x ULN to 5x ULN	Modify the dose of the concomitant MTX if appropriate Interrupt Actemra dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN
> 5x ULN	Discontinue Actemra.

	The decision to discontinue Actemra in sJIA or pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low absolute neutrophil count (ANC)

Laboratory Value (cells x 10^9/ L)	**Action**
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt Actemra dosing When ANC increases to > 1 x 10^9/ L resume Actemra
ANC < 0.5	Discontinue Actemra The decision to discontinue Actemra in sJIA or pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low platelet count

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

Reduction of tocilizumab dosing frequency due to laboratory abnormalities has not been studied in sJIA or pJIA patients.

The safety and efficacy of Actemra subcutaneous formulation in children with conditions other than sJIA or pJIA have not been established.

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

Missed dose

If a sJIA patient misses a subcutaneous weekly injection of Actemra within 7 days of the scheduled dose, he/she should be instructed to take the missed dose on the next scheduled day. If a patient misses a subcutaneous once every 2 week injection of Actemra within 7 days of the scheduled dose, he/she should be instructed to take the missed dose immediately and the next dose on the next scheduled day.

If a pJIA patient misses a subcutaneous injection of Actemra within 7 days of the scheduled dose, he/she should take the missed dose as soon as they remember and take the next dose at the regular scheduled time. If a patient misses a subcutaneous injection of Actemra by more than 7 days of the scheduled dose or is unsure when to inject Actemra, call the doctor or pharmacist.

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

The pre-filled syringe should not be shaken.

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

4.3 Contraindications

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

Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

Actemra subcutaneous formulation is not intended for intravenous administration.

Actemra subcutaneous formulation is not intended to be given to children with sJIA weighing less than 10 kg.

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

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

Vigilance for the timely detection of serious infection is recommended for patients receiving immunosuppressive agents such as Actemra as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute phase reactants. The effects of tocilizumab on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients (which includes younger children with sJIA or pJIA who may be less able to communicate their symptoms) and parents/guardians of sJIA or pJIA patients, should be instructed to contact their healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

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

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

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

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

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

Active hepatic disease and hepatic impairment
Treatment with Actemra, particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases, therefore, caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment (see sections 4.2 and 4.8).

Hepatotoxicity
Transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with Actemra treatment (see section 4.8). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with Actemra. When clinically indicated, other liver function tests including bilirubin should be considered.

Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, have been observed with Actemra (see section 4.8). 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. Patients should be advised to immediately seek medical help if they experience signs and symptoms of hepatic injury.

Caution should be exercised when considering initiation of Actemra treatment in patients with elevated ALT or AST > 1.5 x ULN. In patients with baseline ALT or AST > 5 x ULN, treatment is not recommended.

In RA, GCA, 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 modifications, including Actemra discontinuation, based on transaminases levels see section 4.2. For ALT or AST elevations > 3–5 x ULN, Actemra treatment should be interrupted.

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

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

Severe neutropenia may be associated with an increased risk of serious infections, although there has been no clear association between decreases in neutrophils and the occurrence of serious infections in clinical trials with Actemra to date.

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

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

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

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

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

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

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

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

Population pharmacokinetic analyses did not detect any effect of MTX, non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids on Actemra clearance in RA patients. In GCA patients, no effect of cumulative corticosteroid dose on Actemra exposure was observed.

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

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

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

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

Actemra should not be used during pregnancy unless clearly necessary.

Breast-feeding
It is unknown whether tocilizumab is excreted in human breast milk. The excretion of Actemra in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Actemra should be made taking into account the benefit of breast-feeding to the child and the benefit of Actemra therapy to the woman.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety profile comes from 4510 patients exposed to Actemra in clinical trials; the majority of these patients were participating in adult RA studies (n=4009), while the remaining experience comes from

GCA (n=149), pJIA (n=240) and sJIA (n=112) studies. The safety profile of Actemra across these indications remains similar and undifferentiated.

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

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

Tabulated list of adverse reactions

ADRs from clinical trials and/or post marketing experience with Actemra based on spontaneous case reports, literature cases and cases from non-interventional study programs are listed in Table 1 and are presented by MedDRA system organ class. The corresponding frequency category for each AR is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) rare (≥1/10,000 to <1/1,000) or very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. List of ADRs occurring in patients treated with Actemra

MedDRA System Organ Class	**Frequency categories with preferred terms**			
	Very Common	**Common**	**Uncommon**	**Rare**
Infections and infestations	Upper respiratory tract infections	Cellulitis, Pneumonia, Oral herpes simplex, Herpes zoster	Diverticulitis	
Blood and lymphatic system disorders		Leukopenia, Neutropenia, Hypofibrinogenaemia		
Immune system disorders				Anaphylaxis (fatal)[1,2,3]
Endocrine disorders			Hypothyroidism	
Metabolism and nutrition disorders	Hypercholesterolaemia*		Hypertriglyceridaemia	
Nervous system disorders		Headache, Dizziness		
Eye disorders		Conjunctivitis		
Vascular disorders		Hypertension		
Respiratory, thoracic and mediastinal disorders		Cough, Dyspnoea		
Gastrointestinal disorders		Abdominal pain, Mouth ulceration, Gastritis	Stomatitis, Gastric ulcer	
Hepatobiliary disorders				Drug-induced liver injury, Hepatitis, Jaundice, Very rare: Hepatic failure
Skin and subcutaneous tissue disorders		Rash, Pruritus, Urticaria		Stevens-Johnson-Syndrome[3]

MedDRA System Organ Class	Frequency categories with preferred terms			
	Very Common	**Common**	**Uncommon**	**Rare**
Renal and urinary disorders			Nephrolithiasis	
General disorders and administration site conditions	Injection site reaction	Peripheral oedema Hypersensitivity reaction,		
Investigations		Hepatic transaminases increased, Weight increased, Total bilirubin increased*		

* Includes elevations collected as part of routine laboratory monitoring (see text below)
[1] See section 4.3
[2] See section 4.4
[3] This adverse reaction was identified through post marketing surveillance but not observed in controlled 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.

Subcutaneous use

RA

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

Injection site reactions

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

Immunogenicity

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

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

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

Haematological abnormalities:

Neutrophils

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

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

Platelets
During routine laboratory monitoring in the Actemra 6-month clinical trial SC-I, none of the patients on the SC weekly dose had a decrease in platelet count to ≤50 × 10^3 / μL.

Hepatic transaminase elevations
During routine laboratory monitoring in the Actemra 6-month controlled clinical trial SC-I, elevation in ALT or AST ≥3 x ULN occurred in 6.5% and 1.4% of patients, respectively on the subcutaneous weekly dose.

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

sJIA (SC)
The safety profile of subcutaneous Actemra was evaluated in 51 paediatric patients (1 to 17 years of age) with sJIA. In general, the adverse drug reactions in patients with sJIA were similar in type to those seen in RA patients (see Undesirable Effects section above).

Infections
The rate of infection in sJIA patients treated with SC Actemra was comparable to sJIA patients treated with IV Actemra.

Injection Site Reactions (ISRs)
In the SC Study (WA28118), a total of 41.2% (21/51) sJIA patients experienced ISRs to Actemra SC. The most common ISRs were erythema, pruritus, pain, and swelling at the injection site. The majority of ISRs reported were Grade 1 events and all ISRs reported were non-serious and none required patient withdrawal from treatment or dose interruption.

Immunogenicity
In the SC Study (WA28118), 46 of the 51 (90.2%) patients tested for anti-tocilizumab antibodies at baseline had at least one post-baseline screening assay result. No patient developed positive anti-tocilizumab antibodies post baseline.

Laboratory Abnormalities
In the 52-week open-label SC Study (WA28118), neutrophil count decrease to below 1 × 10^9/L occurred in 23.5% of patients treated with Actemra SC. Decreases in platelet counts to below 100 × 10^3/μL occurred in 2% of the patients treated with Actemra SC. An elevation in ALT or AST to ≥3 x ULN occurred in 9.8% and 4.0% patients treated with Actemra SC, respectively.

Lipid parameters
In the 52-week open-label SC Study (WA28118), 23.4% and 35.4% 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 study treatment, respectively.

pJIA (SC)

The safety profile of subcutaneous Actemra was also evaluated in 52 paediatric patients with pJIA. The total patient exposure to Actemra in the pJIA all exposure population was 184.4 patient years for IV and 50.4 patient years for SC tocilizumab. 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). A higher frequency of pJIA patients experienced ISRs following SC Actemra injections compared to adult RA.

Infections
In the SC Actemra study, the rate of infection in pJIA patients treated with SC Actemra was comparable with pJIA patients treated with IV Actemra.

Injection Site Reactions
A total of 28.8% (15/52) pJIA patients experienced ISRs to Actemra SC. These ISRs occurred in a 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 non-serious Grade 1 events, and none of the ISRs required patient withdrawal from treatment or dose interruption.

Immunogenicity
In the SC Study 5.8% [3/52] developed positive neutralizing anti-tocilizumab antibodies without developing a serious or clinically significant hypersensitivity reaction. Of these 3 patients, 1 subsequently withdrew from the study. No correlation between antibody development and clinical response or adverse events was observed

Laboratory Abnormalities
During routine laboratory monitoring in the Actemra all exposure population, a decrease in neutrophil count below 1×10^9/L occurred in 15.4% of patients treated with SC Actemra. An elevation in ALT or AST ≥3 x ULN occurred in 9.6% and 3.8% patients treated with Actemra SC, respectively. No patients treated with SC Actemra experienced a decrease in platelet count to $\leq 50 \times 10^3$ / μL.

Lipid parameters
In the SC Study, 14.3% and 12.8% 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 study treatment, respectively.

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

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

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

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

Haematological abnormalities:

Neutrophils

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

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

Hepatic transaminase elevations
During routine laboratory monitoring in the Actemra 12 month controlled clinical trial, elevation in ALT ≥3 x ULN occurred in 3% of patients in the Actemra subcutaneous weekly group compared to 2% in the placebo plus 52 week prednisone taper group and none in the placebo plus 26 week prednisone taper group. An elevation in AST > 3 ULN occurred in 1% of patients in the Actemra subcutaneous weekly group, compared to no patients in either of the placebo plus prednisone taper groups.

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

Intravenous use
RA
The safety of Actemra 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 4 mg/kg in combination with MTX, 1870 patients received tocilizumab 8 mg/kg in combination with MTX/other DMARDs and 288 patients received tocilizumab 8 mg/kg monotherapy.

The *all exposure* population includes all patients who received at least one dose of Actemra 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.

Description of selected adverse reactions

Infections
In the 6-month controlled studies the rate of all infections reported with Actemra 8 mg/kg plus DMARD treatment was 127 events per 100 patient years compared to 112 events per 100 patient years in the placebo plus DMARD group. In the long-term exposure population, the overall rate of infections with Actemra was 108 events per 100 patient years exposure.

In 6-month controlled clinical studies, the rate of serious infections with Actemra 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 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 pt years. Reported serious infections, some with fatal outcome, included pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis, bacterial arthritis. Cases of opportunistic infections have also been reported.

Interstitial lung disease
Impaired lung function may increase the risk for developing infections. There have been post-marketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Gastrointestinal perforation
During the 6-month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient years with Actemra therapy. In the long-term exposure population the overall rate of gastrointestinal perforation was 0.28 events per 100 patient years. Reports of gastrointestinal perforation on Actemra were primarily reported as complications of diverticulitis including generalised purulent peritonitis, lower gastrointestinal perforation, fistulae and abscess.

Infusion Related Reactions
In the 6-month controlled trials adverse events associated with infusion (selected events occurring during or within 24 hours of infusion) were reported by 6.9% of patients in the tocilizumab 8 mg/kg plus DMARD group and 5.1% of patients in the placebo plus DMARD group. Events reported during the infusion were primarily episodes of hypertension; events reported within 24 hours of finishing an infusion were headache and skin reactions (rash, urticaria). These events were not treatment limiting.

The rate of anaphylactic reactions (occurring in a total of 6/3778patients, 0.2%) was several fold higher with the 4 mg/kg dose, compared to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with 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 studies. These reactions were generally observed during the second to fifth infusions of tocilizumab (see section 4.4). Fatal anaphylaxis has been reported after marketing authorisation during treatment with intravenous Actemra (see section 4.4).

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

Haematological abnormalities:

Neutrophils

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

During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 6-month controlled clinical trials.

Platelets
In the 6-month controlled trials decreases in platelet counts below 100 x 10^3/ µL occurred in 1.7% of patients on Actemra 8 mg/kg plus DMARDs compared to < 1% on placebo plus DMARDs. These decreases occurred without associated bleeding events.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 6-month controlled clinical trials.

Very rare reports of pancytopenia have occurred in the post marketing setting.

Hepatic transaminase elevations
During the 6-month controlled trials transient elevations in ALT/AST > 3 x ULN were observed in 2.1% of patients on Actemra 8 mg/kg compared to 4.9% of patients on MTX and in 6.5% of patients who received 8 mg/kg Actemra plus DMARDs compared to 1.5% of patients on placebo plus DMARDs.

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

During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevation in ALT/AST remained consistent with what was seen in the 6-month controlled clinical trials.

Lipid parameters
During the 6-month controlled trials, increases of lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol have been reported commonly. With routine laboratory monitoring it was seen that approximately 24% of patients receiving Actemra in clinical trials experienced sustained elevations in total cholesterol ≥ 6.2 mmol/ L, with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/ L. Elevations in lipid parameters responded to treatment with lipid-lowering agents.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevations in lipid parameters remained consistent with what was seen in the 6-month controlled trials.

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

Skin Reactions
Rare reports of Stevens-Johnson Syndrome have occurred in the post marketing setting.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Pharmacodynamic effects
In clinical studies with Actemra, rapid decreases in CRP, erythrocyte sedimentation rate (ESR), serum amyloid A (SAA) and fibrinogen were observed. Consistent with the effect on acute phase reactants, treatment with Actemra was associated with reduction in platelet count within the normal range. Increases in haemoglobin levels were observed, through Actemra decreasing the IL-6 driven effects on hepcidin production to increase iron availability. 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.

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

Patients demonstrate a comparable (to healthy subjects) decrease of absolute neutrophil counts following Actemra administration (see section 4.8).

Subcutaneous use

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

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

Clinical response
Study SC-I evaluated patients with moderate to severe active RA who had an inadequate clinical response to their existing rheumatologic therapy, including one or more DMARD(s) where approximately 20% had a history of inadequate response to at least one TNF inhibitor. In SC-I, 1262 patients were randomized 1:1 to receive Actemra subcutaneous 162 mg every week or Actemra intravenous 8 mg/kg every four weeks in combination with non-biologic DMARD(s). The primary endpoint in the study was the difference in the proportion of patients who achieved an ACR20 response at week 24. The results from study SC-I is shown in Table 2.

*Table **2**. ACR responses in study SC-I (% patients) at Week 24*

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

TCZ = tocilizumab

a = Per Protocol Population

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

Radiographic response

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

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

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

Health-related and quality of life outcomes

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

In study SC-II, mean decrease in HAQ-DI from baseline to week 24 was significantly greater for patients treated with Actemra subcutaneous every other week (0.4) versus placebo (0.3). Proportion of patients achieving a clinically relevant improvement in HAQ-DI at week 24 (change from baseline of

≥ 0.3 units) was higher for Actemra subcutaneous every other week (58%) versus placebo (46.8%). SF-36 (mean change in mental and physical component scores) was significantly greater with Actemra subcutaneous group (6.5 and 5.3) versus placebo (3.8 and 2.9).

sJIA (SC)

Clinical Efficacy

A 52-week, open-label, multi-centre, PK/PD and safety study (WA28118) was conducted in paediatric patients with sJIA, aged 1 to 17 years, to determine the appropriate SC dose of Actemra that achieved comparable PK/PD and safety profiles to the IV regimen.

Eligible patients received Actemra dosed according to body weight (BW), with patients weighing ≥30 kg (n=26) dosed with 162 mg of Actemra every week (QW) and patients weighing below 30 kg (n=25) dosed with 162 mg of Actemra every 10 days (Q10D; n=8) or every 2 weeks (Q2W; n=17) for 52 weeks. Of these 51 patients, 26 (51%) were naive to Actemra and 25 (49%) had been receiving Actemra IV and switched to Actemra SC at baseline.

Exploratory efficacy results showed that Actemra SC improved all exploratory efficacy parameters including Juvenile Arthritis Disease Activity Score (JADAS)-71, for TCZ naïve patients and maintained all exploratory efficacy parameters for patients who switched from Actemra IV to Actemra SC treatment over the entire course of the study for patients in both body weight groups (below 30 kg and ≥30 kg).

pJIA (SC)

A 52-week, open-label, multicenter, PK-PD and safety study was conducted in paediatric patients with pJIA, aged 1 to 17 years old, to determine the appropriate subcutaneous dose of Actemra that achieved comparable PK/PD and safety profiles to the IV regimen.

Eligible patients received tocilizumab dosed according to body weight (BW), with patients weighing ≥30 kg (n = 25) dosed with 162 mg of Actemra every 2 weeks (Q2W) and patients weighing below 30 kg (n = 27) dosed with 162 mg of Actemra every 3 weeks (Q3W) for 52 weeks. Of these 52 patients, 37 (71%) were naive to Actemra and 15 (29%) had been receiving Actemra IV and switched to Actemra SC at baseline.

The Actemra SC regimens of 162 mg Q3W for patients weighing below 30 kg and of 162 mg Q2W for patients weighing ≥ 30 kg respectively provide PK exposure and PD responses to support efficacy and safety outcomes similar to those achieved with the approved Actemra IV regimens for pJIA.

Exploratory efficacy results showed that Actemra SC improved median Juvenile Arthritis Disease Activity Score (JADAS)-71 for Actemra naïve patients and maintained the median JADAS-71 for patients who switched from IV to SC Actemra treatment over the entire course of the study for patients in both body weight groups (below 30 kg and ≥ 30 kg).

GCA (SC)

Clinical efficacy

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

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

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

All patients received background glucocorticoid (prednisone) therapy. Each of the Actemra-treated groups and one of the placebo-treated groups followed a pre-specified prednisone-taper regimen over 26

weeks, while the second placebo-treated group followed a pre-specified prednisone-taper regimen over 52 weeks, designed to be more in keeping with standard practice.

The duration of glucocorticoid therapy during screening and before Actemra (or placebo) was initiated, was similar in all 4 treatment groups (see Table 3).

Table 3. Duration of Corticosteroid Therapy During Screening in Study WA28119

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

The primary efficacy endpoint assessed by the proportion of patients achieving steroid free sustained remission at week 52 on Actemra plus 26 weeks prednisone taper compared with placebo plus 26 weeks prednisone taper, was met (Table 4).

The key secondary efficacy endpoint also based on the proportion of patients achieving sustained remission at week 52, comparing tocilizumab plus 26 weeks prednisone taper with placebo plus 52 weeks prednisone taper, was also met (Table 4).

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

The percentage of patients achieving sustained remission at week 52, are shown in the Table 4.

Secondary Endpoints
The assessment of the time to first GCA flare showed a significantly lower risk of flare for the Actemra subcutaneous weekly group compared to placebo plus 26 weeks prednisone and placebo plus 52 weeks prednisone taper groups and for the Actemra subcutaneous every other weekly group compared to placebo plus 26 weeks prednisone (when compared at a 0.01 significance level). Actemra subcutaneous weekly dose also showed a clinically meaningful decrease in the risk for flare compared to placebo plus 26 weeks prednisone in patients who entered the trial with relapsing GCA as well as those with new-onset disease (Table 4).

Cumulative glucocorticoid dose
The cumulative prednisone dose at week 52 was significantly lower in the two Actemra dose groups compared to the two placebo groups (Table 4). In a separate analysis of the patients who received escape prednisone to treat GCA flare during the first 52 weeks, the cumulative prednisone dose varied greatly. The median doses for escape patients in the Actemra weekly and every other weekly groups were 3129.75 mg and 3847 mg, respectively. Both considerably lower than in the placebo plus 26 weeks and the placebo plus 52 weeks prednisone taper groups, 4023.5 mg and 5389.5 mg respectively.

Table 4. Efficacy results from Study WA28119

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

* p<0.0001
** p<0.005 (threshold for significance for primary and key secondary tests of superiority)
***Descriptive p value <0.005
****Flare: recurrence of GCA signs or symptoms and/or ESR ≥30 mm/h – Increase in the prednisone dose required
Remission: absence of flare and normalization of the CRP
Sustained remission: remission from week 12 to week 52 –Patients must adhere to the protocol-defined prednisone taper
[1] analysis of the time (in days) between clinical remission and first disease flare
[2] p-values are determined using a Van Elteren analysis for non-parametric data
[§] statistical analyses has not been performed
N/A= Not applicable
HR = Hazard Ratio
CI = Confidence Interval

Quality of Life Outcomes

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

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

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

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

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

Intravenous use

RA

Clinical efficacy

The efficacy of Actemra in alleviating the signs and symptoms of RA was assessed in five randomised, double-blind, multi-centre studies. Studies I-V enrolled patients ≥ 18 years of age with active RA diagnosed according to the American College of Rheumatology (ACR) criteria and who had at least eight tender and six swollen joints at baseline.

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

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

Study II, a two year study with planned analyses at week 24, week 52 and week 104, evaluated 1196 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of Actemra or placebo were given every four weeks as blinded therapy for 52 weeks in combination with stable MTX (10 mg to 25 mg weekly). After week 52, all patients could receive open-label treatment with Actemra 8 mg/kg. Of the patients who completed the study who were originally randomised to

placebo + MTX, 86% received open-label Actemra 8 mg/kg in year 2. The primary endpoint at week 24 was the proportion of patients who achieved an ACR 20 response. At week 52 and week 104 the co-primary endpoints were prevention of joint damage and improvement in physical function.

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

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

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

Clinical response

In all studies, patients treated with Actemra 8 mg/kg had statistically significant higher ACR 20, 50, 70 response rates at 6 months compared to control (Table 5). In study I, superiority of Actemra 8 mg/kg was demonstrated against the active comparator MTX.
The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race, number of prior treatments or disease status. Time to onset was rapid (as early as week 2) and the magnitude of response continued to improve with duration of treatment. Continued durable responses were seen for over 3 years in the open label extension studies I-V.

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

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

In a pooled analysis of studies II, III and IV, the proportion of patients achieving an ACR 20, 50 and 70 response was significantly higher (59% vs. 50%, 37% vs. 27%, 18% vs. 11%, respectively) in the tocilizumab 8 mg/kg plus DMARD vs. the tocilizumab 4 mg/kg plus DMARD group ($p< 0.03$). Similarly the proportion of patients achieving a DAS 28 remission (DAS28 < 2.6) was significantly higher (31% vs. 16% respectively) in patients receiving Actemra 8 mg/kg plus DMARD than in patients receiving Actemra 4 mg/kg plus DMARD ($p< 0.0001$).

Table 5. ACR responses in placebo-/MTX-/DMARDs-controlled studies (% patients)

	Study I AMBITION		**Study II LITHE**		**Study III OPTION**		**Study IV TOWARD**		**Study V RADIATE**	
Week	**TCZ 8 mg/kg**	**MTX**	**TCZ 8 mg/kg + MTX**	**PBO + MTX**	**TCZ 8 mg/kg + MTX**	**PBO + MTX**	**TCZ 8 mg/kg + DMARD**	**PBO + DMARD**	**TCZ 8 mg/kg + MTX**	**PBO + MTX**
	N = 286	**N = 284**	**N = 398**	**N = 393**	**N = 205**	**N = 204**	**N = 803**	**N = 413**	**N = 170**	**N = 158**
ACR 20										
24	70%***	52%	56%***	27%	59%***	26%	61%***	24%	50%***	10%
52			56%***	25%						
ACR 50										
24	44%**	33%	32%***	10%	44%***	11%	38%***	9%	29%***	4%
52			36%***	10%						
ACR 70										
24	28%**	15%	13%***	2%	22%***	2%	21%***	3%	12%**	1%
52			20%***	4%						

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

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

Radiographic response
In Study II, in patients with an inadequate response to MTX, inhibition of structural joint damage was assessed radiographically and expressed as change in modified Sharp score and its components, the erosion score and joint space narrowing score. Inhibition of joint structural damage was shown with significantly less radiographic progression in patients receiving Actemra compared to control (Table 6).

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

Table 6. Radiographic mean changes over 52 weeks in Study II

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

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

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

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

Haemoglobin levels
Statistically significant improvements in haemoglobin levels were observed with Actemra 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.

Actemra versus adalimumab in monotherapy
Study VI (WA19924), a 24 week double-blinded study that compared Actemra monotherapy with adalimumab monotherapy, evaluated 326 patients with RA who were intolerant of MTX or where continued treatment with MTX was considered inappropriate (including MTX inadequate responders). Patients in the Actemra arm received an intravenous (IV) infusion of Actemra (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 7).

Table 7: Efficacy Results for Study VI (WA19924)

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

[a] p value is adjusted for region and duration of RA for all endpoints and additionally baseline value for all continuous endpoints.
[b] Non-responder Imputation used for missing data. Multiplicity controlled using Bonferroni-Holm Procedure

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

5.2 Pharmacokinetic properties

The pharmacokinetics of Actemra is characterized by nonlinear elimination which is a combination of linear clearance and Michaelis-Menten elimination. The nonlinear part of Actemra elimination leads to an increase in exposure that is more than dose-proportional. The pharmacokinetic parameters of Actemra do not change with time. Due to the dependence of total clearance on Actemra serum concentrations, the half-life of Actemra 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.

<u>RA</u>
<u>Intravenous use</u>
The pharmacokinetics of Actemra were determined using a population pharmacokinetic analysis on a database composed of 3,552 RA patients treated with a one-hour infusion of 4 or 8 mg/kg Actemra every 4 weeks for 24 weeks or with 162 mg tocilizumab given subcutaneously either once a week or every other week for 24 weeks.

The following parameters (predicted mean ± SD) were estimated for a dose of 8 mg/kg Actemra given every 4 weeks: steady-state area under curve (AUC) = 38000 ± 13000 h•µg/mL, trough concentration (Cmin) = 15.9 ± 13.1 µg/mL and maximum concentration (Cmax) = 182 ± 50.4 µg/mL, and. the

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

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

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

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

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

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

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

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

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

Elimination
For subcutaneous administration, the effective $t_{1/2}$ is up to 13 days for 162 mg every week and 5 days for 162 mg every other week in patients with RA at steady-state.

sJIA

Subcutaneous Use

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), 162 mg SC every week (patients weighing ≥30 kg), 162 mg SC every 10 days or every 2 weeks (patients weighing below 30 kg).

Limited data are available regarding exposures following subcutaneous administration of Actemra in sJIA patients below 2 years of age with a body weight less than 10 kg.
Patients with sJIA must have a minimum body weight of 10 kg when receiving Actemra subcutaneously (see section 4.2).

Table 8. Predicted mean ± SD PK parameters at steady-state after SC dosing in sJIA

Actemra PK Parameter	**162 mg QW ≥ 30 kg**	**162 mg Q2W below 30 kg**
C_{max} (µg/mL)	99.8 ± 46.2	134 ± 58.6
C_{min} (µg/mL)	79.2 ± 35.6	65.9 ± 31.3
C_{mean} (µg/mL)	91.3 ± 40.4	101 ± 43.2
Accumulation C_{max}	3.66	1.88
Accumulation C_{min}	4.39	3.21
Accumulation C_{mean} or AUC_{τ}*	4.28	2.27

*τ = 1 week or 2 weeks for the two SC regimens

After SC dosing, approximately 90% of the steady-state was reached by week 12 for both the 162 mg QW and Q2W regimens.

Absorption

Following SC dosing in sJIA patients, the absorption half-life was around 2 days, and the bioavailability for the SC formulation in sJIA patients was 95%.

Distribution

In paediatric 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

Elimination

The total clearance of tocilizumab was concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 5.7 mL/h in paediatric patients with systemic juvenile idiopathic arthritis. Following subcutaneous administration, the effective $t_{1/2}$ of Actemra in sJIA patients is up to 14 days for both the 162 mg QW and Q2W regimens during a dosing interval at steady state.

pJIA

Subcutaneous use

The pharmacokinetics of Actemra in pJIA patients was characterized by a population pharmacokinetic analysis which included 237 patients who were treated with 8 mg/kg IV every 4 weeks (patients weighing ≥ 30 kg), 10 mg/kg IV every 4 weeks (patients weighing below 30 kg), 162 mg SC every 2 weeks (patients weighing ≥ 30 kg), or 162 mg SC every 3 weeks (patients weighing below 30 kg).

Table 9. Predicted mean ± SD PK parameters at steady-state after SC dosing in pJIA

Actemra PK Parameter	**162 mg Q2W ≥ 30 kg**	**162 mg Q3W below 30 kg**
C_{max} (µg/mL)	29.4 ± 13.5	75.5 ± 24.1
C_{min} (µg/mL)	11.8 ± 7.08	18.4 ± 12.9
C_{avg} (µg/mL)	21.7 ± 10.4	45.5 ± 19.8
Accumulation C_{max}	1.72	1.32
Accumulation C_{min}	3.58	2.08
Accumulation C_{mean} or AUC_{τ} *	2.04	1.46

*τ = 2 week or 3 week for the two SC regimens

After 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. After SC dosing, approximately 90% of the steady-state was reached by Week 12 for both the 162 mg SC Q2W and Q3W regimens.

Absorption

Following SC dosing in pJIA patients, the absorption half-life was around 2 days, and the bioavailability for the SC formulation in pJIA patients was 96%.

Distribution

In paediatric patients with pJIA, the central volume of distribution was 1.97 L, the peripheral volume of distribution was 2.03 L, resulting in a volume of distribution at steady state of 4.0 L.

Elimination

Population pharmacokinetic analysis for pJIA patients showed body size related impact on linear clearance so that body-weight based dosing should be taken into consideration (see Table 9).

After subcutaneous administration, the effective $t_{1/2}$ of Actemra in pJIA patients is up to 10 days for patients < 30 kg (162 mg SC Q3W) and up to 7 days for patients >= 30 kg (162 mg SC Q2W) during a dosing interval at steady state. Following intravenous administration, tocilizumab undergoes biphasic elimination from the circulation. The total clearance of tocilizumab was concentration-dependent and is the sum of the linear and non-linear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 6.25 mL/h. The concentration-dependent non-linear clearance plays a major role at low tocilizumab concentrations. Once the non-linear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.

GCA

Subcutaneous use

The PK of Actemra in GCA patients were determined using a population PK model from an analysis dataset composed of 149 GCA patients treated with 162 mg subcutaneous every week or 162 mg subcutaneous every other week. The developed model had the same structure as the population PK model developed earlier based on data from RA patients (see Table 10).

Table 10. Predicted mean ± SD PK parameters at steady-state after subcutaneous dosing in GCA

	Subcutaneous	
Tocilizumab PK Parameter	**162 mg every other weekly**	**162 mg weekly**
C_{max} (µg/mL)	19.3 ± 12.8	73 ± 30.4
C_{min} (µg/mL)	11.1 ± 10.3	68.1± 29.5
C_{mean} (µg/mL)	16.2 ± 11.8	71.3 ± 30.1
Accumulation C_{max}	2.18	8.88
Accumulation C_{min}	5.61	9.59
Accumulation C_{mean} or AUC_{τ} *	2.81	10.91

*τ = 2 week or 1 week for the two SC regimens

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

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

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

Absorption

Following subcutaneous dosing in GCA patients, the absorption t½ was around 4 days. The bioavailability for the SC formulation was 0.8. The median values of T_{max} were 3 days after the Actemra weekly dose and 4.5 days after the tocilizumab every other week dose.

Distribution

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

Elimination

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

In GCA patients, at steady state, the effective t ½ of Actemra varied between 18.3 and 18.9 days for 162 mg weekly regimen, and between 4.2 and 7.9 days for 162 mg every other weekly regimen. At high serum concentrations, when total clearance of Actemra is dominated by linear clearance, an effective t ½ of approximately 32 days was derived from the population parameter estimates.

Special populations

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

Most of the patients in the RA and GCA studies population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (estimated creatinine clearance based on Cockcroft-Gault formula) did not impact the pharmacokinetics of Actemra.

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

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

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

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

Results of the population PK analysis for sJIA and pJIA patients confirmed that body size is the only covariate which has an appreciable impact on the pharmacokinetics of Actemra including elimination and absorption so that body-weight based dosing should be taken into consideration (see Tables 8 and 9).

5.3 Preclinical safety data

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

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C). Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light and moisture.
Once removed from the refrigerator, the pre-filled syringe can be stored up to 2 weeks (14 days) at or below 30°C. The pre-filled syringe must always be kept in the carton.

6.5 Nature and contents of container

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

Pack sizes of 1 or 4* pre-filled syringes.
*It is possible that not all packs sizes will be marketed

6.6 Special precautions for disposal and other handling

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

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

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

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

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

7. MARKETING AUTHORISATION HOLDER

Roche Pharmaceuticals (Israel) Ltd., P.O.Box 6391 Hod Hasharon 4524079, www.roche.co.il

8. MARKETING AUTHORISATION NUMBER(S)

153-15-34111-00

9. MANUFACTURER

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

Revised on September 2022 according to MOHs guidelines.