NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Actemra® 20 mg/mL, concentrate for solution for intravenous (IV) infusion

Actemra® 162 mg/0.9 mL, solution for subcutaneous (SC) injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Concentrate for solution for IV infusion

Each vial contains 20 mg/mL tocilizumab (vials: 80 mg tocilizumab in 4 mL, 200 mg tocilizumab in 10 mL and 400 mg tocilizumab in 20 mL).

Solution for SC injection

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Actemra concentrated solution for IV infusion is a clear to opalescent, colourless to pale yellow sterile solution.

Actemra solution for SC injection is a clear to strongly opalescent, colourless to slightly yellowish sterile solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid Arthritis (IV and SC formulations)

Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients:

- in combination with methotrexate (MTX) in those not previously treated with MTX;
- in combination with methotrexate (MTX) or other non-biological disease-modifying anti-rheumatic drugs (DMARDs) in case of either an inadequate response or intolerance to previous therapy with one or more DMARDs; or
- as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Actemra has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given alone or in combination with methotrexate.

Giant Cell Arteritis (SC formulation only)

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

Polyarticular Juvenile Idiopathic Arthritis (pJIA) (IV formulation only)

Actemra is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older who have shown an inadequate response to methotrexate (MTX) or were intolerant to MTX. Actemra can be given alone or in combination with MTX.

Systemic Juvenile Idiopathic Arthritis (IV formulation only)
Actemra is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Actemra can be given alone or in combination with methotrexate (MTX).

4.2 Dose and method of administration

General
Treatment should be initiated by healthcare professionals experienced not only in the diagnosis and treatment of RA, GCA, pJIA or sJIA but also in the use of biological therapies for this condition.

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

For adult patients with GCA, Actemra is administered as a SC injection.

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

Actemra IV formulation is not intended for SC administration. Actemra SC formulation is not intended for IV administration.

Actemra should be diluted by a healthcare professional with sterile 0.9% w/v sodium chloride solution using aseptic technique (see section 4.2, Method of Administration).

The recommended duration of the IV infusion is 1 hour.

During IV infusion, and for 30 minutes post-infusion with Actemra, the patient must be closely monitored at all times for any signs or symptoms of a hypersensitivity reaction. Should any such reaction occur then appropriate urgent responses and treatments are to be initiated. The necessary equipment, treatments and protocols sufficient to initiate the management of acute anaphylaxis are to be in place along with the availability of appropriately trained personnel. There must be continued education and training of the health care professionals who administer the infusions. As part of the informed consent process patients should be made aware of the risk of anaphylaxis and the equipment, treatments and protocols in place to manage this risk.

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

Dose

Rheumatoid Arthritis in Adults (IV and SC formulation)
Intravenous dosing regimen
The recommended dose of Actemra for adult patients is 8 mg/kg given once every 4 weeks as an IV infusion.

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

Actemra can be used alone or in combination with MTX and/or other non-biological DMARDs.

Subcutaneous dosing regimen
The recommended dose for adult patients is 162 mg given once every week as a subcutaneous injection.

Actemra can be used alone or in combination with MTX and/or other non-biological DMARDs.

Patients transitioning from IV Actemra 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 healthcare professional.

The first injection should be performed under the supervision of a qualified healthcare professional. After proper training in injection technique, patients may self-inject with Actemra if their treating healthcare professional determines that it is appropriate.

Assess suitability of patient for SC home use and instruct patients to inform a healthcare professional if they experience any symptoms of allergic reaction. Patients should seek immediate medical attention if they develop symptoms of serious allergic reactions (see section 4.4, Hypersensitivity Reactions).

Dose Modification Recommendations for RA
Liver enzyme abnormalities

Lab Value	**Action**
> 1 to 3 x ULN	Dose modify concomitant DMARDs if appropriate For patients receiving intravenous Actemra with persistent increases in this range, reduce Actemra dose to 4 mg/kg or interrupt Actemra until ALT/AST have normalized Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate. For patients receiving subcutaneous Actemra with persistent increases in this range, reduce Actemra injection frequency to every other week or interrupt Actemra until ALT/AST have normalized. Restart with weekly injection or injection every other week, 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, discontinue Actemra (confirmed by repeat testing, see Precautions – Hepatic Transaminase and Laboratory Effects),
> 5 x ULN	Discontinue Actemra

Low absolute neutrophil count (ANC)

Lab Value (cells x 10^9/L)	**Action**
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt Actemra dosing For patients receiving intravenous Actemra, when ANC > 1 x 10^9/L resume Actemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate. For patients receiving subcutaneous Actemra, when ANC > 1 x 10^9/L resume Actemra injection every other week and increase frequency to every week, as clinically appropriate.
ANC < 0.5	Discontinue Actemra

Low platelet count

Lab Value (cells x 10^9/L)	**Action**
50 to 100	Interrupt Actemra dosing For patients receiving intravenous Actemra, when platelet count is > 100 x 10^9/L resume Actemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate. For patients receiving subcutaneous Actemra, when platelet count is > 100 x 10^9/L resume Actemra injection every other week and increase frequency to every week, as clinically appropriate.
< 50	Discontinue Actemra

Giant Cell Arteritis (SC formulation only)

The recommended dose of Actemra for adult patients with GCA is 162 mg given once every week as a subcutaneous injection, in combination with a tapering course of glucocorticoids. Actemra can be used alone following discontinuation of glucocorticoids.

In the event of patients experiencing a relapse of GCA during the course of Actemra therapy, the treating physician should consider re-introducing and/or escalating the dose of concomitant glucocorticoids (or restarting glucocorticoid therapy if it has been discontinued) according to best medical judgement/treatment guidelines.

The first injection should be performed under the supervision of a qualified healthcare professional. After proper training in injection technique, patients may self-inject with Actemra if their treating healthcare professional determines that it is appropriate.

Assess suitability of patient for SC home use and instruct patients to inform a healthcare professional if they experience any symptoms of allergic reaction. Patients should seek immediate medical attention if they develop symptoms of serious allergic reactions (see section 4.4, Hypersensitivity Reactions).

Dose Modification Recommendations for GCA
Liver enzyme abnormalities

Lab Value	Action
> 1 to 3x ULN	Dose modify concomitant immunomodulatory agents if appropriate. For patients with persistent increases in this range, reduce Actemra injection frequency to every other week or interrupt Actemra until ALT/AST have normalised. Restart with weekly injection or injection every other week, as clinically appropriate.
> 3 to 5x ULN	Interrupt Actemra dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN For persistent increases > 3x ULN (confirmed by repeat testing, see section 4.4, Hepatic Transaminase and Laboratory Effect), discontinue Actemra.
> 5x ULN	Discontinue Actemra.

Low absolute neutrophil count (ANC)

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

Low platelet count

Lab Value (cells x 10^9/L)	Action
50 to 100	Interrupt Actemra dosing When platelet count is > 100 x 10^9/L resume Actemra injection every other week and increase frequency to every week, as clinically appropriate.
< 50	Discontinue Actemra.

Polyarticular Juvenile Idiopathic Arthritis (pJIA) (IV formulation only)
The recommended dose of Actemra for patients with pJIA is:
- 10 mg/kg for patients below 30 kg,
- 8 mg/kg for patients ≥ 30 kg,

given once every four weeks as an IV infusion. 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.

Systemic Juvenile Idiopathic Arthritis (IV formulation only)
The recommended dose of Actemra for patients with sJIA is:
- 12 mg/kg for patients below 30 kg,
- 8 mg/kg for patients ≥ 30 kg,

given once every two weeks as an IV infusion. 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.

Dose Modification Recommendations for pJIA and sJIA
Dose reduction of Actemra has not been studied in the pJIA or sJIA population. Dose interruptions of Actemra for laboratory abnormalities are recommended in patients with pJIA or sJIA and are similar to what is outlined above for patients with RA (see section 4.4, Haematological Abnormalities). If appropriate, concomitant MTX and/or other medications should be dose modified or stopped and Actemra dosing interrupted until the clinical situation has been evaluated. In pJIA or sJIA the decision to discontinue Actemra for a laboratory abnormality should be based upon the medical assessment of the individual patient.

Special populations

Paediatric Populations
The safety and efficacy in paediatric patients below the age of 2 years old have not been established.

Elderly
No dose adjustment is required in elderly patients aged 65 years and older.

Renal impairment
No dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2, Pharmacokinetics in Special Populations). Actemra has not been studied in patients with severe renal impairment.

Hepatic impairment
The safety and efficacy of Actemra has not been studied in patients with hepatic impairment (see section 4.4, Active Hepatic Disease and Hepatic Impairment) and therefore no dose recommendations can be made.

Method of Administration
Concentrated solution for intravenous infusion
Parenteral medications should be inspected visually for particulate matter or discolouration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles must be infused.

Rheumatoid Arthritis
From a 100 mL infusion bag, withdraw a volume of 0.9% sodium chloride solution equal to the volume of the Actemra solution required for the patient's dose, and discard. Withdraw the required amount of Actemra (0.4 mL per kg of the patient's body weight) under aseptic conditions and add to the infusion bag. To mix the solution, gently invert the bag to avoid foaming.

sJIA patients below 30 kg
From a 50 mL infusion bag, withdraw a volume of 0.9% sodium chloride solution equal to 0.6 mL/kg of the patient's body weight and discard. This volume should be replaced in the saline bag with an equal volume of Actemra under aseptic conditions. To mix the solution, gently invert the bag to avoid foaming.

pJIA patients below 30 kg
From a 50 mL infusion bag, withdraw a volume of 0.9% sodium chloride solution equal to 0.5 mL/kg of the patient's body weight and discard. This volume should be replaced in the

saline bag with an equal volume of Actemra under aseptic conditions. To mix the solution, gently invert the bag to avoid foaming.

pJIA and sJIA patients ≥ 30 kg
From a 100 mL infusion bag, withdraw a volume of 0.9% sodium chloride solution equal to the volume of the Actemra solution required for the patient's dose. Withdraw the required amount of Actemra (0.4 mL per kg of the patient's body weight) under aseptic conditions and dilute in a 100 mL infusion bag containing sterile, non-pyrogenic 0.9% sodium chloride solution. To mix the solution, gently invert the bag to avoid foaming.

Solution for Subcutaneous Injection
Subcutaneous Actemra formulation is administered with a single-use pre-filled syringe.

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.

If a patient misses a weekly injection of Actemra within 7 days of the scheduled dose, they should be instructed to take the missed dose on the next scheduled day. If a patient misses a biweekly (i.e. every other week) injection of Actemra within 7 days of the scheduled dose, they should be instructed to take the missed dose immediately and the next dose on the next scheduled day.

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.

Actemra should not be shaken.

After removing the pre-filled syringe from the refrigerator, the pre-filled syringe should be allowed to reach room temperature by waiting for 25 to 30 minutes, before injecting. After removing the cap the injection should be started within 5 minutes.

4.3 Contraindications
Actemra is contraindicated in patients with:

- known hypersensitivity to any component of the product or with a history of any reaction consistent with hypersensitivity to any component of the product, Chinese hamster ovary cell products or other recombinant human or humanised antibodies
- active, severe infections (see section 4.4, Infections)

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

All Indications

Infections

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

Vigilance for the timely detection of serious infection is recommended for patients receiving immunosuppressive agents, such as Actemra, for moderate to severe RA, GCA, pJIA or sJIA as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute phase reaction. The effects of Actemra 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 include younger children who may be less able to communicate their symptoms) and parents/guardians of minors with pJIA or sJIA should be instructed to contact a physician immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

The use of Actemra is not recommended in patients with HIV, positive core antibody for hepatitis B, prior HCV infection, or symptomatic EBV infection. Viral reactivation (e.g. hepatitis B) has been reported with biologic therapies for RA. In clinical studies with Actemra, patients who screened positive for hepatitis were excluded.

In the long term RA exposure population, the overall rate of serious infections (bacterial, viral and fungal) was 4.7 events per 100 patient years. Reported serious infections, some with fatal outcome, included active tuberculosis, which may present with intrapulmonary or extrapulmonary disease, invasive pulmonary infections, including candidiasis, aspergillosis, coccidioidomycosis and pneumocystis jirovecii, pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported.

Complications of Diverticulitis

Events of diverticular perforation as complications of diverticulitis have been reported in patients treated with Actemra. Actemra should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, should be evaluated promptly for early identification of gastrointestinal perforation.

Tuberculosis

As recommended for other biological treatments for 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.

Vaccinations

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

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

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.

In a randomised 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.

Hypersensitivity Reactions
Serious hypersensitivity reactions, including anaphylaxis, have been reported in association with Actemra (see section 4.8, Infusion Reactions). In the post-marketing setting, events of serious hypersensitivity and anaphylaxis, have occurred in patients treated with a range of doses of Actemra, with or without concomitant therapies, premedication and/or a previous hypersensitivity reaction.

In the post marketing setting, cases with a fatal outcome have been reported with intravenous Actemra. These events have occurred as early as the first infusion of Actemra (see section 4.3 and 4.8, Post-Marketing Experience). Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during infusion with Actemra. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of Actemra should be stopped immediately and Actemra should be permanently Discontinued.

Patients with a history of any reaction consistent with hypersensitivity to any component of the product must not be re-challenged with Actemra (see section 4.3).

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.

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, Special Populations and section 4.8, Laboratory Abnormalities).

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

Hepatotoxicity
Mild and moderate elevations of hepatic transaminases and bilirubin have been reported 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. There is a potential risk of hepatotoxicity with use of Actemra.

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.

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

In RA, GCA, pJIA and sJIA, ALT /AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended dose modifications, including Actemra discontinuation, based on transaminases levels, see section 4.2.

For ALT or AST elevations > 3 to 5 x ULN, confirmed by repeat testing, Actemra treatment should be interrupted. Once the patient's hepatic transaminases are below 3 x ULN, treatment with Actemra may recommence at 4 or 8 mg/kg for the IV formulation or weekly injection or injection every other week for the SC formulation.

Haematological Abnormalities

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

Caution should be exercised when considering initiation of Actemra treatment in patients with a low neutrophil or platelet count (i.e. ANC < 2 x 10^9/L or platelet count below 100 x 10^9/L). In patients with an ANC below 0.5 x 10^9/L or a platelet count < 50 x 10^9/L treatment is not recommended (see section 4.4, Effects of Laboratory Tests).

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

Lipid Parameters

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

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

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

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

Intravenous Infusion Reactions
Infusion reactions have been observed during and within 24 hours of treatment with Actemra (see section 4.8, Infusion Reactions).

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 (see section 4.4, Lipid Parameters). Elevations in LDL and HDL lipids have been observed, with no clinical consequences identified. No data are available concerning cardiovascular outcomes with long-term use of Actemra.

Combination with TNF Antagonists and/or other Biological Therapies
There is no experience with the use of Actemra with TNF antagonists or other biological treatments for RA. Actemra is not recommended for use with other biologic agents including TNF antagonists, anakinra, rituximab and abatacept.

Sodium
Intravenous Actemra contains 1.17 mmol (26.55 mg) of sodium per maximum dose of 1200 mg. This should be taken into consideration by patients on a controlled sodium diet. Doses below 1025 mg of Actemra contain less than 1 mmol of sodium (23 mg) and can essentially be considered 'sodium free'.

The subcutaneous Actemra formulation does not contain sodium.

Use in Children
The safety and efficacy in paediatric patients below the age of 2 years old have not been established.
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.

Use in the Elderly
Population analyses evaluated the potential effects of demographic characteristics on the pharmacokinetics of Actemra in adult RA patients. Results of these analyses showed that no adjustment of the dose is necessary for age, gender, or race.

No dose adjustment is required in elderly patients.

Effects on Laboratory Tests
Caution should be exercised when considering initiation of Actemra treatment in patients with a low neutrophil count. Decreases in neutrophil counts below 1 x 10^9/L occurred in 3.4%, with counts < 0.5 x 10^9/L occurring in 0.3%, of patients on Actemra 8 mg/kg + DMARD without clear association with serious infection (see section 4.4, Haematological

Abnormalities and 4.8, Laboratory Abnormalities). In patients with an absolute neutrophil count < 0.5 x 10^9/L treatment is not recommended.

Systemic Juvenile Idiopathic Arthritis

Macrophage activation syndrome (MAS)

MAS is a serious life-threatening disorder that may develop in patients with sJIA. In clinical trials, Actemra has not been studied in patients during an episode of active MAS (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

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

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.

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

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

In vitro studies with cultured human hepatocytes demonstrated that IL-6 caused a reduction in CYP3A4 and to a lesser extent CYP1A2, CYP2C9 and CYP2C19 enzyme messenger RNA (mRNA) expression. Tocilizumab was shown to normalise expression of the mRNA for these enzymes.

This is clinically relevant for CYP450 substrates with a narrow therapeutic index, and/or where the dose is individually adjusted.

In a study in RA patients, levels of simvastatin and its acid metabolite (CYP3A4 substrates) were decreased by 57% and 39%, respectively, one week following a single dose of tocilizumab, to a level similar or slightly higher than those observed (in other studies) in healthy subjects.

When starting or stopping therapy with Actemra, patients taking medicinal products which are individually adjusted and are metabolised via CYP450 3A4, 1A2, 2C9 or 2C19 (e.g. atorvastatin, dextromethorphan, omeprazole, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporine or benzodiazepines) should be monitored as doses may need adjustment to maintain therapeutic effect. The degree of dose uptitration upon initiation of therapy or dose down-titration when stopping therapy with Actemra should be based on the therapeutic response and/or adverse effects of the patient to the individual medicine. Given a relatively long elimination half-life ($t_{1/2}$), the effect of Actemra on CYP450 activity may persist for several weeks after stopping therapy.

No drug-drug interaction studies have been conducted in sJIA patients.

4.6 Fertility, pregnancy and lactation

Pregnancy – Category C
Actemra should not be used during pregnancy unless clearly necessary. There are no adequate data from the use of Actemra in pregnant women. The potential risk for humans is unknown. Women of childbearing potential should be advised to use adequate contraception during and for several months after therapy with Actemra.

In an embryo-foetal toxicity study conducted in cynomolgus monkeys, a slight increase of abortion/embryo-foetal death was observed with high systemic cumulative exposure in the 10 mg/kg/day mid-dose group (> 35 times human exposure) and in the 50 mg/kg/day high-dose group (> 100 times human exposure) compared to vehicle control and low-dose groups. It cannot be excluded that this finding is related to Actemra treatment. Placental transfer of both tocilizumab and anti-tocilizumab antibodies to the foetus was seen in cynomolgus monkeys.

Breast-feeding
It is unknown whether tocilizumab is excreted in human breast milk and its efficacy and safety in lactating women has not been established. However, it is known that endogenous immunoglobulins of the IgG isotype are excreted into human milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Actemra should be made taking into account the benefit of breast-feeding to the child and the benefit of Actemra therapy to the woman.

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

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, there is no evidence from the available data that Actemra treatment affects the ability to drive and use machines.

4.8 Undesirable effects

All indications
The safety profile in this section comes from 4458 patients exposed to Actemra in clinical trials; the majority of these patients were participating in RA studies (n = 4009), while the remaining experience comes from pJIA (n = 188), sJIA (n = 112), and GCA (n = 149) studies. The safety profile of Actemra across these indications remains similar and undifferentiated.

Adverse Drug Reactions (ADRs) from clinical trials (Table 1) are listed by MedDRA system organ class according to clinical importance to the patient. The corresponding requency

category for each ADR is based on the following convention: very common (≥1/10), common (≥1/100 to < 1/10) or uncommon (≥1/1000 to < 1/100).

Table 1 Summary of ADRs occurring in patients treated with Actemra

System Organ Class	Very Common	Common	Uncommon
Infections and infestations	Upper respiratory tract infections	Cellulitis, oral herpes simplex, herpes zoster	Diverticulitis
Gastrointestinal disorders	-	Abdominal pain, mouth ulceration, gastritis	Stomatitis, gastric ulcer
Skin and subcutaneous tissue disorders	-	Rash, pruritus, urticaria	-
Nervous system disorders	-	Headache, dizziness	-
Investigations	-	Hepatic transaminases increased, weight increased	Total bilirubin increased
Vascular disorders	-	Hypertension	-
Blood and lymphatic system disorders	-	Leucopenia, neutropenia	-
Metabolism and nutrition disorders	-	Hypercholesterolaemia	Hypertriglyceridemia
General disorders and administration site conditions	-	Peripheral oedema, hypersensitivity reaction, injection site reaction	-
Respiratory, thoracic and mediastinal disorders	-	Cough, dyspnoea	-
Eye disorders	-	Conjunctivitis	-
Renal disorders	-	-	Nephrolithiasis
Endocrine disorders	-	-	Hypothyroidism

Description of selected adverse drug reactions from clinical trials:

Rheumatoid Arthritis

Patients Treated with Intravenous Actemra

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 randomisation until either the first change in the treatment regimen, or 2 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 Actemra 8 mg/kg in combination with MTX/other DMARDs and 288 patients received Actemra 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. The mean duration of exposure to Actemra in the *all exposure* population was 2.14 years.

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

In the 6 month controlled clinical trials, the rate of serious infections (bacterial, viral and fungal) with Actemra 8 mg/kg + DMARD was 5.3 events per 100 pt years exposure compared to 3.9 events per 100 pt years exposure in the placebo + DMARD group. In the monotherapy study the rate of serious infections was 3.6 events per 100 pt years of exposure in the Actemra group and 1.5 events per 100 pt 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 and 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 (GI) perforation was 0.26 events per 100 pt years with Actemra therapy. In the *all exposure* population the overall rate of GI perforation was 0.28 events per 100 pt years. Reports of GI perforation were primarily reported as complications of diverticulitis including generalised purulent peritonitis, lower GI perforation, fistula and abscess.

Infusion Reactions
In the 6 month controlled trials adverse events associated with infusion (selected events occurring during or within 24 hours of infusion) were reported by 6.9% of patients in the Actemra 8 mg/kg + DMARD and 5.1% of patients in the placebo + 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.

In the 6 month controlled clinical trials, the rate of anaphylactic reactions in those receiving the lower dose of 4 mg/kg was 3/744 (0.4%) and in the higher dose of 8 mg/kg was 3/1870 (0.2%). As anaphylactic reactions tend to occur early in the course of treatment, the overall rate of anaphylaxis cumulatively in the long term extensions remained at 6/3778 or 0.2%.

Clinically significant hypersensitivity reactions associated with Actemra and requiring treatment discontinuation, were reported in a total of 13 out of 3778 patients (0.3%) treated with Actemra during the controlled and open label clinical trials. These reactions were generally observed during the second to fifth infusions of Actemra (see section 4.4, Hypersensitivity Reactions).

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

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

Early Rheumatoid Arthritis
Study VIII (FUNCTION) evaluated 1162 patients with early, moderate to severe RA who were naïve to treatment with both MTX and a biologic agent. The overall safety profile observed in the Actemra treatment groups was consistent with the known safety profile of Actemra (Table 1).

In study VI the rate of withdrawal due to adverse events was higher in the Actemra plus MTX and Actemra monotherapy groups compared to MTX alone. The withdrawals were mainly due to elevations in liver enzymes (see section 4.8, Laboratory Abnormalities).

Monotherapy: Actemra versus adalimumab
In a 24 week double-blinded, parallel study (monotherapy with Actemra 8 mg/kg IV q4w (n = 162) compared to adalimumab 40 mg SC q2w (n=162)), the overall clinical AE profile was similar between Actemra and adalimumab. The proportion of patients with serious AEs was balanced between the treatment groups (Actemra 11.7% vs. adalimumab 9.9%) with the most common event being infections (3.1% each). Both study treatments induced the same pattern of changes in laboratory safety parameters (decreases in neutrophil and platelet counts, increases in alanine transaminase (ALT), aspartate transaminase (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 low-density lipoprotein (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 Actemra arm was consistent with the known safety profile of Actemra and no new or unexpected adverse drug reactions were observed.

Patients Treated with Subcutaneous Actemra
The safety of subcutaneous Actemra was studied in Study VI (SUMMACTA). The study compared the efficacy and safety of Actemra 162 mg administered every week SC versus 8 mg/kg IV in 1262 subjects with adult RA. All patients in the study received background non-biologic DMARDs. The safety and immunogenicity observed for Actemra administered SC was consistent with the known safety profile of IV 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 SC arms compared with placebo SC injections in the IV arms.

Injection Site Reactions
During the 6-month controlled period in SUMMACTA, the frequency of injection site reactions was 10.1% (64/631) and 2.4% (15/631) for the subcutaneous Actemra and the placebo SC (IV 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 SUMMACTA, a total of 625 patients treated with Actemra 162 mg weekly were tested for anti-tocilizumab antibodies in the 6 month controlled period. Five patients (0.8%) developed

positive anti-tocilizumab antibodies; of these, all developed neutralizing anti-tocilizumab antibodies.

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

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

Giant Cell Arteritis
The safety of subcutaneous Actemra was studied in 251 GCA patients in a Phase III study (Study X, GiACTA). 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) versus 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.

Polyarticular Juvenile Idiopathic Arthritis
The safety of intravenous Actemra was studied in 188 paediatric patients, 2 to 17 years of age, with pJIA. The total patient exposure in the Actemra all exposure population was 184.4 pt years. In general, with the exception of MAS, the types of adverse drug reactions (ADRs) in patients with pJIA were similar to those seen in RA and sJIA patients.

Infections
The rate of infections in the Actemra all exposure population was 163.7 per 100 pt years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was 4.9 per 100 pt years.

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

No clinically significant hypersensitivity reactions were reported.

Immunogenicity

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

Systemic Juvenile Idiopathic Arthritis
The safety of intravenous Actemra in sJIA has been studied in 112 paediatric patients 2 to 17 years of age. In the 12 week double-blind, controlled portion of the clinical trial 75 patients received treatment with Actemra (8 or 12 mg/kg based upon body weight). After 12 weeks or at the time of escape, due to disease worsening, patients were treated in the on-going open-label extension phase.

In general, the ADRs in patients with sJIA were similar in type to those seen in RA and pJIA patients (see section 4.8, Rheumatoid Arthritis).

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

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

In Australia, a case of fatal sepsis occurred in a 6-year old who had been treated with Actmera for approximately 2 years for sJIA. Methotrexate was given concomitantly. The patient had symptoms of gastroenteritis on the day preceding his death, and the last dose of Actemra was administered 10 days prior to the event. The death was assessed as related to septicaemia.

Macrophage Activation Syndrome
In the 12 week controlled study, no patient in any treatment group experienced macrophage activation syndrome (MAS) while on assigned treatment. Three per 112 (3%) developed MAS during open-label treatment with Actemra. One patient in the placebo group escaped to Actemra 12 mg per kg at Week 2 due to severe disease activity, and ultimately developed MAS at Day 70. Two additional patients developed MAS during the long-term extension. All 3 patients had Actemra dose interrupted (2 patients) or discontinued (1 patient) for the MAS event, received treatment, and the MAS resolved without sequelae. Based on a limited number of cases, the incidence of MAS does not appear to be elevated in the Actemra sJIA clinical development experience, however no definitive conclusions can be made.

A case of MAS with a fatal outcome was reported in a patient enrolled in a clinical study of Actemra in sJIA. The patient had interrupted Actemra treatment 4 weeks prior to the onset of MAS because of a rotavirus infection. The patient also experienced a worsening of sJIA prior to the diagnosis of MAS.

Infusion Reactions
For sJIA patients, infusion related reactions are defined as all events occurring during or within 24 hours of an infusion. In the 12 week controlled trial, 4.0% of patients from the Actemra group experienced events occurring during infusion, one event (angioedema) was

considered serious and life-threatening, and the patient was discontinued from study treatment.

In the 12 week controlled trial experience, 16% of patients in the Actemra group and 5.4% of patients in the placebo group experienced an event within 24 hours of infusion. In the Actemra group, the events included, but not limited to rash, urticaria, diarrhoea, epigastric discomfort, arthralgia and headache. One of these events (urticaria) was considered serious.

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

Reports of anaphylaxis, anaphylactoid reactions, and hypersensitivity reactions in patients under 18 years of age have been reported in the post-marketing setting.

Immunogenicity
All 112 patients were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti-tocilizumab antibodies with one of these patients having a hypersensitivity reaction leading to withdrawal.

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

Laboratory Abnormalities
Haematology Abnormalities
Rheumatoid Arthritis
Neutrophils – Intravenous Administration
In the 6 month controlled trials decreases in neutrophil counts below 1 x 10^9/L occurred in 3.4% of patients on Actemra 8 mg/kg + DMARD compared to < 0.1% of patients on placebo + DMARD. 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 + DMARD (see section 4.4, Effects on Laboratory Tests).

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

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

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

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

Platelets – Intravenous Administration

In the 6 month controlled trials decreases in platelet counts below 100 x 10^9/L occurred in 1.7% of patients on Actemra 8 mg/kg + DMARDs compared to < 1% on placebo + DMARDs. These decreases occurred without associated bleeding events (see section 4.2 and section 4.4, Haematological Abnormalities.)

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

Platelets – Subcutaneous Administration
During routine laboratory monitoring in the Actemra 6-month controlled period of SUMMACTA, none of the patients had a decrease in platelet count to ≤ 50 x 10^9/L.

Giant Cell Arteritis
Neutrophils
During routine laboratory monitoring in the Actemra 12-month double blind, placebo-controlled phase of Study X (GiACTA), a decrease in neutrophil count below 1 x 10^9/L occurred in 4% of patients in the Actemra weekly group. This was not observed in either of the placebo plus prednisone taper groups. 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 12-month double blind, placebo-controlled phase of Study X (GiACTA), one patient (1%, 1/100) in the Actemra weekly group had a single transient occurrence of decreased platelet count below 100 x 10^9/L without associated bleeding events. A decrease in platelet count below 100 x 10^9/L was not observed in either of the placebo plus prednisone taper groups.

Polyarticular Juvenile Idiopathic Arthritis
Neutrophils
During routine laboratory monitoring in the Actemra all exposure population, a decrease in neutrophil count below 1 × 10^9/L occurred in 3.7% of patients. 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 all exposure population, 1% of patients had a decrease in platelet count to ≤ 50 × 10^3/μL without associated bleeding events.

Systemic Juvenile Idiopathic Arthritis
Neutrophils
During routine laboratory monitoring in the 12 week controlled trial, a decrease in neutrophil counts below 1 × 10^9/L occurred in 7% of patients in the Actemra group, and in none in the placebo group. In the ongoing open-label extension study decreases in neutrophil counts below 1 x 10^9/L occurred in 15% of patients in the Actemra group.

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 12 week controlled trial, 3% of patients in the placebo group and 1% in the Actemra group had a decrease in platelet count to ≤ 100 × 10^3/μL. In the ongoing open-label extension study decreases in platelet counts below 100 x 10^3/μL occurred in 3% of patients in the Actemra group, without associated bleeding events.

Liver Enzyme Elevations

Rheumatoid Arthritis

Intravenous Administration

During the 6 month controlled trials transient elevations in ALT (alanine transaminase)/AST (aspartate transaminase) > 3 x ULN (Upper Limit of Normal) 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 Actemra 8 mg/kg + DMARD compared to 1.5% of patients on placebo + DMARD. The addition of potentially hepatotoxic drugs (for example 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 + DMARD patients, the majority of whom were discontinued from Actemra treatment. During routine laboratory monitoring, the incidence of indirect bilirubin > ULN is 6.2% in patients treated with 8 mg/kg Actemra + DMARD in the *all control* population.

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

In Study WA25204 (ENTRACTE), of the 1538 patients with moderate to severe RA (see Section 5.1) and treated with Actemra, elevations in ALT or AST >3 x ULN occurred in 5.3% and 2.2% patients, respectively. One serious event of drug induced hepatitis with hyperbilirubinemia was reported in association with Actemra treatment (see section 4.4).

Subcutaneous Administration

During routine laboratory monitoring in the Actemra 6-month controlled period of SUMMACTA, elevation in ALT or AST ≥ 3 x ULN occurred in 6.5% and 1.4% of patients, respectively on the SC weekly dose

Early Rheumatoid Arthritis

In Study VI, MTX-naïve adult patients with moderate to severe, active early RA (mean disease duration ≤ 6 months) experienced more transient elevations in ALT > 3 x ULN compared with the all control population. This was observed in both Actemra treated patients and MTX monotherapy patients.

Giant Cell Arteritis

During routine laboratory monitoring in the Actemra 12-month double blind, placebo-controlled phase of Study X (GiACTA), elevation in ALT ≥ 3 ULN occurred in 3% of patients in the Actemra weekly group compared to 2% in the placebo plus 52 week prednisone taper group and none in the placebo plus 26 weeks prednisone taper group. An elevation in AST > 3 ULN occurred in 1% of patients in the Actemra weekly group, compared to no patients in either of the placebo plus prednisone taper group.

Polyarticular Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the Actemra all exposure population, elevation in ALT or AST ≥ 3 x ULN occurred in 3.7% and <1% of patients, respectively.

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

In the ongoing open-label extension study, elevation in ALT or AST ≥ 3 x ULN occurred in 12% and 4% of patients, respectively, in the tocilizumab group.

Elevations in Lipid Parameters
Rheumatoid Arthritis
Intravenous Administration
During routine laboratory monitoring in the 6 month controlled trials, increases of lipid parameters such as total cholesterol, triglycerides, LDL (low-density lipoprotein) cholesterol, and/or HDL (high-density lipoprotein) cholesterol have been commonly reported. Approximately 24% of patients receiving Actemra in clinical trials experienced sustained elevations in total cholesterol above 6.2 mmol/L (240 mg/dL), with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/L (160 mg/dL). Elevations in lipid parameters responded to treatment with lipid-lowering agents.

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

Subcutaneous Administration
During routine laboratory monitoring in the Actemra 6-month controlled period of SUMMACTA, 19% of patients on the SC weekly dose 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 SC weekly dose.

Giant Cell Arteritis
During routine laboratory monitoring in the Actemra 12-month double blind, placebo-controlled phase of Study X (GiACTA), 25% of patients experienced elevations in total cholesterol above 6.2 mmol/L (240 mg/dL), with 47% experiencing an increase in LDL to ≥ 4.1 mmol/L (160 mg/dL) in the Actemra weekly group.

Polyarticular Juvenile Idiopathic Arthritis
During routine laboratory monitoring in the Actemra all exposure population, the highest post-baseline values for total cholesterol were > 1.5-2 x ULN in one patient (0.5%) and for LDL > 1.5-2 x ULN in one patient (0.5%).

Systemic Juvenile Idiopathic Arthritis
During routine laboratory monitoring in the 12 week controlled trial, elevation in total cholesterol >1.5 x ULN to 2 x ULN occurred in 1.5% of the Actemra group and in 0% of placebo patients. Elevation in LDL >1.5 x ULN to 2 x ULN occurred in 1.9% of patients in the Actemra group and 0% of the placebo group.

In the ongoing open-label extension study the pattern and incidence of elevations in lipid parameters remained consistent with the 12 week controlled trial data.

Post-Marketing Experience
The following adverse drug reactions have been identified from post marketing experience with tocilizumab (Table 2) based on spontaneous case reports, literature cases and cases from

non-interventional study programs. Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 2: Adverse drug reactions from post marketing experience

Adverse reaction (MedDRA)	Incidence	Frequency Category
Immune system disorders		
Anaphylaxis (fatal)[1, 2]	Not observed in clinical trials	Rare
Skin and subcutaneous tissue disorders		
Stevens-Johnson syndrome[3]	Not observed in clinical trials	Rare
Hypofibrinogenemia	1.3 per 100 patient years	Common
Blood and lymphatic system disorders		
Hepatobiliary disorders		
Drug-induced liver injury	0.2 per 100 patient years	Rare
Hepatitis	0.035 per 100 patient years	Rare
Hepatic failure	0.004 per 100 patient years	Very rare
Jaundice[4]	Not observed in clinical trials	Rare

[1] See section *4.3 Contraindications*
[2] See section *4.4 Special warnings and precautions for use*
[3] This adverse reaction was identified through post marketing surveillance but not observed in clinical trials. The frequency category was estimated as the upper limit of the 95% confidence interval calculated on the basis of the total number of patients exposed to tocilizumab in clinical trials.
[4] Incidence rate calculated based on all-exposure data obtained from relevant completed clinical trials for all indications

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/}

4.9 Overdose
There are limited data available on overdosage with Actemra. One case of accidental overdose was reported in which a patient with multiple myeloma received a single dose of 40 mg/kg IV. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received a single dose up to 28 mg/kg IV, although dose-limiting neutropenia was observed.

Treatment of overdose should consist of general supportive measures.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors; ATC code: L04AC07.

Mechanism of Action
Tocilizumab is a recombinant humanised monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass which binds to human interleukin 6 (IL-6) receptors. It is composed of two heterodimers, each of which consists of a heavy and a light polypeptide chain. The light chain contains of 214 amino acids and the heavy chain 448 amino acids. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. Tocilizumab has a molecular weight of approximately 148,000 Daltons. Tocilizumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R).

Tocilizumab binds to both soluble and membrane-bound IL-6 receptors, and has been shown to inhibit sIL-6R and mIL-6R-mediated signaling. IL-6 is a multi-functional cytokine, produced by a variety of cell types involved in local paracrine function as well as regulation of systemic physiological and pathological processes such as induction of immunoglobulin secretion, T-cell activation, induction of hepatic acute phase proteins and stimulation of haematopoiesis. IL-6 has been implicated in the pathogenesis of diseases including rheumatoid arthritis (RA).

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

Pharmacodynamic effect
In clinical studies with Actemra in RA, rapid decreases in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and serum amyloid A were observed. Rapid increases in haemoglobin levels (within the first 2 weeks) were also observed, through Actemra decreasing the IL-6 driven effects on hepcidin production to increase iron availability.

In patients with giant cell arteritis (GCA), 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, absolute neutrophil counts (ANC) decreased to their lowest levels 3 to 5 days following administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. Patients with RA demonstrated a similar pattern of absolute neutrophil counts following Actemra administration (see section 4.4, Haematological Abnormalities).

Clinical efficacy and safety
Rheumatoid Arthritis
The efficacy of intravenous Actemra in alleviating the signs and symptoms of RA was assessed in five randomised, double-blind, multicentre studies (Studies I – V). The efficacy of subcutaneous Actemra was assessed in two randomised, double-blind studies (Studies VI and VII). In addition, the efficacy of intravenous Actemra has been evaluated in patients with MTX-naïve, early RA (Study VIII) and as a monotherapy versus adalimumab monotherapy (Study IX).

Intravenous Administration
Studies I-V required patients ≥ age 18 with active RA diagnosed according to American College of Rheumatology (ACR) criteria who had at least 8 tender and 6 swollen joints at baseline.

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

Study I (AMBITION) evaluated 673 patients who had not been treated with MTX within 6 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 to a maximum of 20 mg weekly over an 8 week period). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24. Inclusion criteria included discontinuation of etanercept for ≥2 weeks, infliximab or adalimumab for ≥8 weeks, anakinra for ≥1 week, leflunomide for ≥12 weeks (or ≥4 weeks after 11 days of standard cholestyramine washout) prior to randomisation, had received MTX for at least 12 weeks immediately prior to baseline (including a stable dose between 10-25 mg/week for the last 8 weeks prior to baseline), all DMARDs withdrawn prior to baseline, SJC (Swollen Joint Count) of ≥6 (66 joint count) and TJC (Tender Joint Count) of ≥8 (68 joint count) at screening and baseline, oral corticosteroids (≤10 mg/day prednisone or equivalent) and NSAIDs (up to the maximum recommended dose) were permitted if the dose was stable for at least 6 weeks prior to baseline. Exclusion criteria included treatment with MTX within 6 months prior to randomisation, discontinuation of previous MTX treatment due to clinically important toxicity or lack of response (determined by investigator), unsuccessful treatment with an anti-TNF agent due to significant safety issues or lack of efficacy, known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections, absolute neutrophil count <2 x 10^9/L. (Not all inclusion or exclusion criteria are listed.)

Study II (LITHE), a 2 year study, 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 – 25 mg weekly). The primary endpoint at week 24 was the proportion of patients who achieved ACR20 response criteria. At week 52 the co-primary endpoints were prevention of joint damage and improvement in physical function. Inclusion criteria for Study II were the same as the criteria listed above for Study I with the exception that all DMARDs other than MTX were withdrawn prior to baseline. In addition radiographic evidence of at least one joint with definite erosion attributable to RA was required (all relevant joints were considered with the exception of the distal inter-phalangeal joints of the hands). Exclusion criteria included unsuccessful treatment with an anti-TNF agent due to significant safety issues or lack of efficacy, known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections, absolute neutrophil count < 2 x 10^9/L. (Not all inclusion or exclusion criteria are listed.)

Study III (OPTION) evaluated 623 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, in combination with stable MTX (10 – 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24. Inclusion criteria for Study III were the same as the criteria listed above for Study I with the exception that all DMARDs other than MTX were withdrawn prior to baseline. Exclusion criteria included unsuccessful treatment with an anti-TNF agent due to significant safety issues or lack of efficacy, known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections, absolute neutrophil count <2 x 10^9/L. (Not all inclusion or exclusion criteria are listed.)

Study IV (TOWARD) evaluated 1220 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 the stable DMARD. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24. Inclusion criteria for Study IV included discontinuation of etanercept for ≥2 weeks, infliximab or adalimumab for ≥8 weeks, anakinra for ≥1 week prior to randomisation, has received permitted DMARDs at a stable dose for at least 8 weeks prior to baseline, SJC (66 joint count) of ≥6 and TJC (68 joint count) of ≥8 at screening and baseline, oral corticosteroids (≤10 mg/day prednisone or equivalent) and NSAIDs (up to the maximum recommended dose) were permitted if the dose was stable for at least 6 weeks prior to baseline. Exclusion criteria included unsuccessful treatment with an anti-TNF agent due to significant safety issues or lack of efficacy, known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections, absolute neutrophil count <2 x 10^9/L. (Not all inclusion or exclusion criteria are listed.)

Study V (RADIATE) evaluated 499 patients who had an inadequate clinical response or were intolerant to one or more anti-tumour necrosis factor (TNF) therapies. The anti-TNF agent was discontinued prior to randomisation. Doses of 4 or 8 mg/kg of Actemra or placebo were given every four weeks, in combination with stable MTX (10 – 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24. Inclusion criteria for Study V were the same as the criteria listed for Study I above with the exception that all DMARDs other than MTX were withdrawn prior to baseline, and that within 1 year prior to randomisation the patient experienced an inadequate response to treatment with etanercept, infliximab, or adalimumab due to toxicity or inadequate efficacy. Exclusion criteria included known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections, absolute neutrophil count <2 x 10^9/L. (Not all inclusion or exclusion criteria are listed).

The percent of patients achieving ACR 20, 50 and 70 responses in Studies I to V are shown in Table 3.

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

	Study I MTX-Naïve		**Study II Inadequate Response to MTX**		**Study III Inadequate Response to MTX**		**Study IV Inadequate Response to DMARD**		**Study V Inadequate Response to anti-TNF Agent**	
Response Rate	**ACT 8 mg/kg n=286**	**MTX n=284**	**ACT 8 mg/kg +MTX n=398**	**Placebo + MTX n=393**	**ACT 8 mg/kg +MTX n=205**	**Placebo + MTX n=204**	**ACT 8mg/kg + DMARD n=803**	**Placebo + DMARD n=413**	**ACT 8 mg/kg +MTX n=170**	**Placebo + MTX n=158**
ACR 20										
Week 24	70%***	52%	56%***	27%	59%***	26%	61%***	24%	50%***	10%
Week 52^			56%***	25%						
ACR 50										
Week 24	44%**	33%	32%***	10%	44%***	11%	38%***	9%	29%***	4%
Week 52^			36%***	10%						
ACR 70										
Week 24	28%**	15%	13%***	2%	22%***	2%	21%***	3%	12%**	1%

Week 52^			20%***	4%						
MCR† by Week 52^			7%	1%						

ACT = Actemra; * *p<0.05, Actemra vs. placebo+MTX/DMARD;* ** *p<0.01*, *Actemra vs. placebo+MTX/DMARD;* *** *p<0.0001, Actemra vs. placebo+MTX/DMARD*; † MCR = major clinical response, defined as an ACR70 response maintained for any 24 consecutive weeks or more.
Note: the comparison for MCR occurred after the break in the hierarchical ordered testing sequence, so no significance claims can be made. Secondary efficacy endpoints were tested in a fixed sequence approach in order to control for the rate of false positive conclusions.
^ *based on a protocol-specified interim analysis*

In all studies, 8 mg/kg Actemra-treated patients had statistically significant higher ACR20, 50, 70 response rates at 6 months compared to placebo. 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 on going open label extension studies of studies I -V.

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

Actemra 8 mg/kg treated patients had a statistically significant greater reduction in disease activity score (DAS28) than patients treated with placebo + DMARD. The rate of remission (defined as DAS < 2.6) for patients treated with Actemra ranged from 27.5% to 33.6%. Actemra treated patients had a statistically significant greater rate of remission than patients treated with placebo + DMARD. A good to moderate EULAR response was achieved by significantly more Actemra treated patients compared to patients treated with placebo + DMARD (Table 4).

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

	Study I MTX-Naïve		**Study II Inadequate Response to MTX**		**Study III Inadequate Response to MTX**		**Study IV Inadequate Response to DMARD**		**Study V Inadequate Response to anti-TNF Agent**	
	ACT 8 mg/kg n=286	**MTX n=284**	**ACT 8 mg/kg + MTX n=398**	**Placebo + MTX n=393**	**ACT 8 mg/kg + MTX n=205**	**Placebo + MTX n=204**	**ACT 8 mg/kg + DMARD n=803**	**Placebo + DMARD n=413**	**ACT 8 mg/kg + MTX n=170**	**Placebo + MTX n=158**
Change in DAS28 [mean (Adjusted mean (SE))]										
Week 24	-3.31 (0.12)	-2.05 (0.12)	-3.11 (0.09)***	-1.45 (0.11)	-3.43 (0.12)***	-1.55 (0.15)	-3.17 (0.07)***	-1.16 (0.09)	-3.16 (0.14)***	-0.95 (0.22)
DAS<2.6 response (%)										
Week 24	33.6%	12.1%	≠33.3%***	^3.8%	27.5%***	0.8%	30.2%***	3.4%	30.1%***	1.6%

EULAR response (%)										
None	18%	35%	26%	65%	20%	65%	20%	62%	32%	84%
Moderate	42%	48%	34%	29%	41%	32%	40%	33%	31%	15%
Good†	40%	17%	41%***	6%	38%***	3%	40%***	4%	37%***	2%

ACT = Actemra; †The p value compares across all the EULAR categories; ** p<0.05, Actemra vs. placebo+MTX/DMARD; ** p<0.01*, *Actemra vs. placebo+MTX/DMARD; *** p<0.0001*, *Actemra vs. placebo+MTX/DMARD*

≠ In study II, 47% of patients achieved a DAS28 < 2.6 at 52 weeks compared to 33% of patients at week 24. ^ In study II, 8% of patients achieved a DAS28 < 2.6 at 52 weeks compared to 4% of patients at week 24.

Major Clinical Response

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

Radiographic Response

In study II (LITHE), 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 (JSN) score. Missing week 52 radiographic data was imputed using linear extrapolation. This was performed for any patient who had a baseline assessment and at least one post-baseline radiographic assessment. The change from baseline was then calculated using the extrapolated score. Inhibition of structural joint damage was shown with significantly less radiographic progression in patients receiving Actemra compared to control (Table 5).

In the open-label extension of study II further improvement in the inhibition of progression of structural damage in Actemra + MTX-treated patients was observed in the second year of treatment. Study II did not investigate the effect of Actemra monotherapy on radiographic endpoints.

Table 5 Radiographic mean changes at 52 and 104 weeks in study II (LITHE)

	ACT 8 mg/kg + MTX [n=398]	**Placebo + MTX (+ option of ACT from week 16) [n=393]**
Changes from baseline to week 52		
N	353	294
Total Sharp-Genant score	0.25	1.17
Erosion score	0.15	0.76
JSN score	0.10	0.41
Change from week 52 to week 104		
N	353	294
Total Sharp-Genant score	0.12	0.79
Erosion score	0.07	0.48
JSN score	0.05	0.31

ACT = Actemra
JSN = joint space narrowing
The data presented consists of the evaluations of the baseline, week 24, week 52, week 80, week 104 and early withdrawal or escape therapy readings taken up to the week 104 visit.

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

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

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

At week 52, the mean change in HAQ-DI was -0.58 in the Actemra 8 mg/kg + MTX group compared with -0.39 in the placebo + MTX group. The mean change in HAQ-DI was maintained at week 104 in the Actemra 8 mg/kg + MTX group (-0.61). The percentage of

Actemra-treated patients showing a clinically relevant improvement in HAQ-DI (≥ 0.3 units) at weeks 52 & 104 were 63% and 62%, respectively.

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

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

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

Table 6 Efficacy Results for Study VIII (FUNCTION) on MTX-naïve, early RA patients

			ACT 8 mg/kg + MTX n=290	**ACT 8 mg/kg + placebo n=292**	**Placebo + MTX n=287**
Primary Endpoint					
DAS < 2.6 response (%)					
	Week 24		44.8***	38.7***	15.0
Key Secondary Endpoints					
DAS < 2.6 response (%)					
	Week 52		49.0***	39.4	19.5
ACR (%)					
	Week 24	ACR20	74.5)*	70.2	65.2
		ACR50	56.9**	47.6	43.2
		ACR70	38.6**	30.1	25.4

		ACT 8 mg/kg + MTX n=290	ACT 8 mg/kg + placebo n=292	Placebo + MTX n=287
Week 52	ACR20	67.2*	63.0	57.1
	ACR50	55.9**	49.3	40.8
	ACR70	43.1**	36.0	28.9
HAQ-DI (adjusted mean change from baseline)				
Week 52		-0.81*	-0.67	-0.64
Radiographic Endpoints (mean change from baseline)				
Week 52	mTSS[#]	0.08***	0.26	1.14
	Erosion Score	0.05**	0.15	0.63
	JSN	0.03	0.11	0.51
	Radiographic non-progression (%) (change from baseline in mTSS[#] of ≤ 0)	83‡	82‡	73
Exploratory Endpoints				
Week 24: ACR/EULAR Boolean Remission (%)		18.4‡	14.2	10.0
ACR/EULAR Index Remission (%)		28.5‡	22.6	16.4
Week 52: ACR/EULAR Boolean Remission (%)		25.7‡	18.7	15.5
ACR/EULAR Index Remission (%)		36.1‡	30.0	22.4

All efficacy comparisons vs Placebo + MTX. ***p ≤ 0.0001; **p < 0.001; *p < 0.05;
‡p-value < 0.05 vs. Placebo + MTX, but endpoint was exploratory (not included in the hierarchy of statistical testing and has therefore not been controlled for multiplicity)
[#] mTSS = modified Total Sharp score

Monotherapy: Actemra versus adalimumab

Study IX (ADACTA) 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 IX (ADACTA)

	ADA + Placebo (IV) n = 162	ACT + Placebo (SC) n = 163	p-value[(a)]
Primary Endpoint - Mean Change from baseline at Week 24			
DAS28 (adjusted mean)	-1.8	-3.3	
Difference in adjusted mean (95% CI)	-1.5 (-1.8, -1.1)		<0.0001
Secondary Endpoints - Percentage of Responders at Week 24 [(b)]			
DAS28 < 2.6, n (%)	18 (10.5)	65 (39.9)	<0.0001
DAS28 ≤ 3.2, n (%)	32 (19.8)	84 (51.5)	<0.0001

ACR20 response, n (%)	80 (49.4)	106 (65.0)	0.0038
ACR50 response, n (%)	45 (27.8)	77 (47.2)	0.0002
ACR70 response, n (%)	29 (17.9)	53 (32.5)	0.0023

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

Cardiovascular Outcomes

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

The study included 3,080 seropositive RA patients with active disease and an inadequate response to non-biologic disease-modifying anti-rheumatic drugs, who were aged ≥50 years with at least one additional CV risk factor beyond RA. Patients were randomised 1:1 to IV Actemra 8 mg/kg every four weeks (q4w) or SC etanercept 50 mg every week (qw) and followed for an average of 3.2 years. The primary endpoint was the comparison of the time-to-first occurrence of any component of a composite of major adverse CV events (MACE; non-fatal myocardial infarction, non-fatal stroke, or CV death), with the final intent-to-treat analysis based on a total of 161 confirmed CV events reviewed by an independent and blinded adjudication committee.

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

Subcutaneous Administration

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

SUMMACTA evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to their existing rheumatologic therapy, including one or more DMARDs. Approximately 20% had a history of inadequate response to at least one TNF inhibitor. In SUMMACTA, 1262 patients were randomized 1:1 to receive subcutaneous Actemra 162 mg every week or intravenous Actemra 8mg/kg every four weeks in combination with non-biologic DMARDs. 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 SUMMACTA are shown in Table 8.

Table 8 Clinical Response at Week 24 in Subcutaneous Trial (Percent of Patients)

	Study VI (SUMMACTA)[a]	
	ACT SC 162 mg every week + DMARDs	**ACT IV 8 mg/kg every 4 weeks + DMARDs**

	n = 558	n = 537
ACR20		
Week 24	69.4%	73.4%
Weighted difference (95% CI)	-4.0 (-9.2, 1.2)	
ACR50		
Week 24	47.0%	48.6%
Weighted difference (95% CI)	-1.8 (-7.5, 4.0)	
ACR70		
Week 24	24.0%	27.9%
Weighted difference (95% CI)	-3.8 (-9.0, 1.3)	
Change in DAS28 [adjusted mean]		
Week 24	3.5	3.5
Adjusted mean difference (95% CI)	0 (-0.2, 0.1)	
DAS28 < 2.6		
Week 24	38.4%	36.9%
Weighted difference (95% CI)	0.9 (-5.0, 6.8)	
EULAR response (%)		
None	3.3%	4.8%
Moderate	41.7%	42.7%
Good	55.0%	52.4%

ACT = Actemra; [a] = per protocol population

Radiographic Response

The radiographic response of subcutaneously administered Actemra was assessed in Study VII (BREVACTA), a double-blind, controlled, multicentre study in patients with active RA. This study evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to their existing rheumatologic therapy, including one or more DMARDs 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 rheumatoid arthritis diagnosed according to ACR criteria and who had at least 8 tender and 6 swollen joints at baseline. In BREVACTA, 656 patients were randomized 2:1 to subcutaneous Actemra 162 mg every other week or placebo, in combination with non-biologic DMARDs.

In BREVACTA, 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 subcutaneous Actemra compared with placebo [mTSS of 0.62 vs. 1.23, p = 0.0149 (van Elteren)]. These results are consistent with those observed in patients treated with intravenous Actemra.

Quality of Life Outcomes

In SUMMACTA, the mean decrease in HAQ-DI from baseline to week 24 was 0.6 for both subcutaneous Actemra 162 mg weekly and intravenous Actemra 8mg/kg every 4 weeks. The proportion of patients achieving a clinically relevant improvement in HAQ-DI at week 24 (change from baseline of ≥ 0.3 units) was comparable in the subcutaneous Actemra every week group (65.2%) versus the intravenous Actemra 8mg/kg group (67.4%), with a weighted difference in proportions of -2-3% (95% CI -8.1, 3.4). The SF-36 summary was split into mental and physical components. The mental component scores were similar between the groups, with a mean change from baseline at week 24 of 6.22 for the SC group and 6.54 for the IV group. The physical component scores were also similar between the groups, with mean change from baseline at week 24 of 9.49 for the SC group and 9.65 for the IV group.

Giant Cell Arteritis (GCA)
Study X (GiACTA) was a randomised, multicentre, 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 is 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 (SC) 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.

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 9).

Secondary Endpoints
The key secondary efficacy endpoint, also based on the proportion of patients achieving sustained remission at Week 52, comparing Actemra plus 26 weeks prednisone taper with the longer placebo plus 52 weeks prednisone taper, was also met (Table9). 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 Table 9.

The assessment of the time to first GCA flare showed a significantly lower risk of flare for the Actemra weekly group compared to placebo plus 26 weeks prednisone and placebo plus 52 weeks prednisone taper groups and for the Actemra every other week group compared to placebo plus 26 weeks prednisone (when compared at a 0.01 significance level). Actemra 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 9).

The median cumulative prednisone dose at Week 52 was significantly lower in the two Actemra dose groups compared to the two placebo groups (Table 9). 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 week 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 9 Efficacy Results from Study X (GiACTA)

			PBO + 26 weeks pred. taper n = 50	PBO + 52 weeks pred. taper n = 51	TCZ 162mg SC QW + 26 weeks pred. taper n = 100	TCZ 162 mg SC Q2W + 26 weeks pred. taper n = 49
Primary Endpoint						
Sustained remission (TCZ groups vs PBO+26)						
Responders at Week 52, n (%)			7 (14%)	9 (17.6%)	56 (56%)	26 (53.1%)
Unadjusted difference in proportions			N/A	N/A	42%*	39.06%*
(99.5% CI)					(18.00, 66.00)	(12.46 , 65.66)
Key Secondary Endpoint						
Sustained remission (TCZ groups vs PBO+52)						
Responders at Week 52, n (%)			7 (14%)	9 (17.6%)	56 (56%)	26 (53.1%)
Unadjusted difference in proportions			N/A	N/A	38.35%*	35.41%**
(99.5% CI)					(17.89, 58.81)	(10.41, 60.41)
Other Secondary Endpoints						
Time to first GCA flare[1]						
All patients	TCZ vs. PBO+26	HR	N/A	N/A	0.23*	0.28**
		(99% CI)			(0.11, 0.46)	(0.12, 0.66)
	TCZ vs. PBO+52	HR	N/A	N/A	0.39**	0.48
		(99% CI)			(0.18, 0.82)	(0.20, 1.16)
Relapsing patients	TCZ vs. PBO+26	HR	N/A	N/A	0.23***	0.42
		(99% CI)			(0.09,0.61)	(0.14, 1.28)
	TCZ vs. PBO+52	HR	N/A	N/A	0.36	0.67
		(99% CI)			(0.13, 1.00)	(0.21,2.10)
New-onset patients	TCZ vs. PBO+26	HR	N/A	N/A	0.25***	0.20***
		(99% CI)			(0.09, 0.70)	(0.05, 0.76)
	TCZ vs. PBO+52	HR	N/A	N/A	0.44	0.35
		(99% CI)			(0.14, 1.32)	(0.09, 1.42)
Cumulative glucocorticoid dose (mg)						
Median at Week 52 (TCZ groups vs PBO+26[2])			3296	N/A	1862.00*	1862.00**
Median at Week 52 (TCZ groups vs PBO+52[2])			N/A	3817.5	1862.00*	1862.00*
Exploratory Endpoints						
Annualized relapse rate, Week 52[§]						
Mean (SD)			1.74 (2.18)	1.3 (1.84)	0.41 (0.78)	0.67 (1.1)

* p<0.0001; ** p<0.005 (threshold for significance for primary and key secondary tests of superiority) ***Descriptive p value <0.005; [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, TCZ = tocilizumab, PBO = placebo, QW = every week dose, Q2W = every other week dose

Quality of Life Outcomes
In Study X, 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 week 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: 0.86 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 week 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 [p = 0.0252 for weekly, p = 0.1468 for every other week]) 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 week 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 week plus 26 weeks prednisone taper group showed a statistically significance difference compared to placebo [placebo plus 26 weeks taper p = 0.0059, and placebo plus 52 week 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 5.61 [10.115], Actemra every other week 1.81 [8.836], PBO plus 26 weeks 0.26 [10.702], and PBO plus 52 weeks -1.63 [6.753].

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

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

Polyarticular Juvenile Idiopathic Arthritis
The efficacy of Actemra was assessed in a three-part study (Study XI, CHERISH) including an open-label extension in children with active pJIA. Part I consisted of a 16 week active Actemra treatment lead in period (n=188) followed by Part II, a 24 week randomised, double-blind, placebo-controlled withdrawal period (ITT n=163), followed by Part III, a 64 week open-label period. Eligible patients ≥ 30 kg received Actemra at 8 mg/kg for 4 doses. Patients < 30 kg were randomised 1:1 to receive either Actemra 8 mg/kg or 10 mg/kg IV every 4 weeks for 4 doses. Patients who completed Part I of the study and achieved at least a JIA ACR30 response at week 16 compared to baseline entered the blinded withdrawal period (Part II) of the study. In Part II, patients were randomised to Actemra (same dose received in Part I) or placebo in a 1:1 ratio, stratified by concurrent MTX use and concurrent

corticosteroid use. Each patient continued in Part II of the study until Week 40 or until the patient satisfied JIA ACR30 flare criteria (relative to Week 16) and qualified for escape.

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

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

During the withdrawal phase (Part II), the percentages of patients achieving JIA ACR 30, 50, and 70 responses at Week 40 relative to baseline are shown in the table below.

Table 10 JIA ACR response rates at week 40 relative to baseline (percentages of patients)

Response Rate	**Actemra n=82**	**Placebo n=81**
JIA ACR 30	74.4%†	54.3%†
JIA ACR 50	73.2%†	51.9%†
JIA ACR 70	64.6%†	42.0%†

† p<0.001, Actemra vs. placebo

Systemic Juvenile Idiopathic Arthritis

The efficacy of intravenous Actemra for the treatment of active sJIA was assessed in a 12-week randomised, double blind, placebo-controlled, parallel group, 2-arm study (study XII, TENDER). Patients (treated with or without MTX) were randomised (Actemra: placebo = 2:1) to one of two treatment groups. The study inclusion criteria required patients to have had an inadequate clinical response to NSAIDs and corticosteroids due to toxicity or lack of efficacy. 75 patients received Actemra infusions every two weeks either 8 mg/kg for patients ≥ 30kg or 12 mg/kg for patients < 30 kg and 37 patients were assigned to receiving placebo infusions every two weeks. Corticosteroid tapering could occur from week 6 for patients who achieved a JIA ACR70 response. After 12 weeks or at the time of escape, due to disease worsening, patients were treated in the open-label extension phase at weight appropriate dosing.

The demographic characteristics at baseline were similar between the placebo and Actemra groups. Patients were evenly split between male and female, with a median age of 9 and 10 for the placebo and Actemra groups, respectively. 27 patients in the study were aged between 2-5 years, 48 patients between 6-12 years and 37 patients between 13-18 years. Baseline disease characteristics studied included fever and rash status, previous use of DMARDs, previous use of biologics, CRP, and articular and extra-articular damage. All were similar between the placebo and Actemra groups except for a higher proportion of patients with rash in the placebo group (48.6%) compared with the Actemra group (29.3%). In addition, baseline CRP was lower in the placebo group in comparison with the Actemra group.

The primary endpoint was the proportion of patients with at least 30% improvement in JIA ACR core set (JIA ACR30 response) at Week 12 and absence of fever (no temperature recording ≥ 37.5°C in the preceding 7 days). Eighty five percent (64/75) of the patients

treated with Actemra and 24.3% (9/37) of placebo patients achieved this endpoint. These proportions were highly significantly different (p<0.0001).

The percent of patients achieving JIA ACR 30, 50, 70 and 90 responses are shown in the table below.

Table 11 JIA ACR response rates at week 12 (percent of patients)

Response Rate	Actemra n=75	Placebo n=37
ACR 30	90.7%*	24.3%
ACR 50	85.3%*	10.8%
ACR 70	70.7%*	8.1%
ACR 90	37.3%*	5.4%

* p<0.0001, Actemra vs. placebo

Secondary endpoints of the study included the proportion of patients with fever due to sJIA at baseline who were free of fever at week 12, corticosteroid tapering, quality of life improvements as measured by CHAQ-DI and changes in laboratory parameters.

Systemic Features
In those patients treated with Actemra, 85% who had fever due to sJIA at baseline were free of fever (no temperature recording ≥ 37.5°C in the preceding 14 days) at week 12 versus only 21% of placebo patients (p<0.0001), and 64% of Actemra-treated patients with rash characteristic of sJIA at baseline were free of rash at week 12 versus 11% of placebo patients (p=0.0008).

There was a highly statistically significant reduction in pain for Actemra-treated patients at week 12 in comparison to placebo patients. The adjusted mean change in the pain VAS after 12 weeks of Actemra treatment was a reduction of 41 points on a scale of 0 -100 compared to a reduction of 1 for placebo patients (p<0.0001).

Corticosteroid Tapering
Of the 31 placebo and 70 Actemra patients receiving oral corticosteroids at baseline, 8 placebo and 48 Actemra patients achieved a JIA ACR70 response at week 6 or 8 enabling corticosteroid dose reduction. Seventeen (24%) Actemra patients versus 1 (3%) placebo patient were able to reduce the dose of corticosteroid by at least 20% without experiencing a subsequent JIA ACR30 flare or occurrence of systemic symptoms to week 12 (p=0.028).

Quality of Life
At week 12, the proportion of Actemra-treated patients showing a minimally clinically important improvement in CHAQ-DI (defined as an individual total score decrease of ≥0.13) was significantly higher than in patients receiving placebo, 77% versus 19% (p<0.0001).

Laboratory Parameters
Fifty out of 75 (67%) patients treated with Actemra had a haemoglobin < LLN at baseline. Forty (80%) of these patients with decreased haemoglobin had an increase in their haemoglobin to within the normal range at week 12, in comparison to only 2 out of 29 (7%) of placebo patients with haemoglobin < LLN at baseline (p<0.0001). Forty-four (88%) Actemra patients with decreased haemoglobin at baseline had an increase in their haemoglobin by ≥10 g/L at week 6 versus 1 (3%) placebo patient (p<0.0001).

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

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

A Phase I, multi-centre, open-label, single arm study (NP25737) to evaluate the PK, safety and exploratory PD and efficacy of tocilizumab over 12 weeks in paediatric sJIA patients (N=11) under 2 years of age was conducted. Patients (treated with stable background therapy of corticosteroids, MTX, or non-steroidal anti-inflammatory drugs) received intravenous tocilizumab 12 mg/kg every two weeks. Patients who completed the 12-week period could continue to the optional extension period (a total of 52-weeks or until the age of 2 years, whichever was longer).

The primary PK endpoints (C_{max}, C_{min} and AUC_{2weeks}) of tocilizumab at steady-state in this study are within the ranges of these parameters observed in paediatric patients aged 2 to 17 years in Study WA18221.

The types of AEs observed during the 12-week evaluation period of Study NP25737 were consistent with the safety profile observed in the pivotal Phase III study (WA18221). Of the 11 patients aged under 2 years, three experienced serious hypersensitivity reactions, and three developed treatment induced anti-tocilizumab antibodies after the event. However, due to the small sample size, the low number of events and confounding factors, conclusions could not be drawn.

Exploratory efficacy results showed that tocilizumab improved the median JADAS-71 score over the course of the study for all patients. The observed PD responses in sIL6R, CRP, and ESR were also consistent with the pivotal Phase III study.

5.2 Pharmacokinetic properties

Rheumatoid Arthritis

Intravenous Administration

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

The pharmacokinetic parameters of Actemra did not change with time. A more than dose-proportional increase in area under the curve (AUC) and trough concentration (C_{min}) was observed for doses of 4 and 8 mg/kg every 4 weeks. Maximum concentration (C_{max}) increased dose-proportionally. At steady-state, predicted AUC and C_{min} were 2.7 and 6.5 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively.

The following parameters are valid for a dose of 8 mg/kg tocilizumab given every 4 weeks. Predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 35000 ± 15500 •µg•h/mL, 9.74 ± 10.5 µg/mL, and 183 ± 85.6 µg/mL, respectively. The accumulation ratios for AUC and C_{max} were small; 1.22 and 1.06, respectively. The accumulation ratio was higher for C_{min} (2.35), which was expected based on the nonlinear clearance contribution at lower concentrations. Steady-state was reached following the first administration and after 8 and 20 weeks for C_{max}, AUC, and C_{min}, respectively. Tocilizumab AUC, C_{min} and C_{max}

increased with increase of body weight. At body weight ≥ 100 kg, the predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 55500 ± 14100 h·µg/mL, 19.0 ± 12.0 µg/mL, and 269 ± 57 µg/mL, respectively, which are higher than mean exposure values for the patient population. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended in patients ≥ 100 kg (see Dosage and Administration).

The following parameters are valid for a dose of 4 mg/kg tocilizumab given every 4 weeks. Predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 13000 ± 5800•µg•h/mL, 1.49 ± 2.13 µg/mL, and 88.3 ± 41.4 µg/mL, respectively. The accumulation ratios for AUC and C_{max} were small; 1.11 and 1.02, respectively. The accumulation ratio was higher for C_{min} (1.96). Steady-state was reached following the first administration for both C_{max} and AUC and from 16 weeks for C_{min}.

Subcutaneous Administration

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

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

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

Giant Cell Arteritis (GCA)

The pharmacokinetics of tocilizumab in GCA patients were determined using a population pharmacokinetic model from an analysis dataset composed of 149 GCA patients treated with 162 mg SC every week or with 162 mg SC every other week. The developed model had the same structure as the population PK model developed earlier based on data from RA patients.

Table 12 Predicted mean ± SD PK parameters at steady-state after SC dosing in GCA

	SC	
TCZ PK Parameter	**162 mg Q2W**	**162 mg QW**
C_{max} (mcg/mL)	19.3 ± 12.8	73 ± 30.4
C_{trough} (mcg/mL)	11.1 ± 10.3	68.1± 29.5
C_{mean} (mcg/mL)	16.2 ± 11.8	71.3 ± 30.1
Accumulation C_{max}	2.26	8.88
Accumulation C_{trough}	5.61	9.59
Accumulation C_{mean} or AUC_{τ}	2.81	10.91

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

Polyarticular Juvenile Idiopathic Arthritis
The pharmacokinetics of tocilizumab was determined using a population pharmacokinetic analysis on a database composed of 188 patients with polyarticular juvenile idiopathic arthritis (pJIA).

The following parameters are valid for a dose of 8 mg/kg tocilizumab (patients with a body weight ≥ 30 kg) given every 4 weeks. The predicted mean (± SD) AUC_{4weeks}, C_{max} and C_{min} of tocilizumab were 29500 ± 8660 µg•hr/mL, 182 ± 37 µg/mL and 7.49 ± 8.2 µg/mL, respectively.

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

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

Systemic Juvenile Idiopathic Arthritis
The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 75 patients with systemic juvenile idiopathic arthritis (sJIA) treated with 8 mg/kg (patients with a body weight ≥ 30 kg) or 12 mg/kg (patients with a body weight < 30 kg), given every 2 weeks. The predicted mean (± SD) AUC_{2weeks}, C_{max} and C_{min} of tocilizumab were 32200 ± 9960 µg•hr/mL, 245 ± 57.2 µg/mL and 57.5 ± 23.3 µg/mL, respectively. The accumulation ratio for C_{min} (week12/week2) was 3.2 ± 1.3. The tocilizumab C_{min} was stabilised after week 12. Mean predicted tocilizumab exposure parameters were similar between the two body weight groups.

The pharmacokinetics of tocilizumab were similar in paediatric patients under 2 years compared to patients over 2 years of age with a body weight below 30 kg from a regimen of 12 mg/kg IV tocilizumab given every 2 weeks.

Absorption and Bioavailability
Following SC dosing in RA and GCA patients, the absorption half-life was around 4 days. The bioavailability for the SC formulation was 0.8.

In GCA patients, the median values of T_{max} were 3 days after the tocilizumab weekly dose and 4.5 days after the tocilizumab every other week dose.

Distribution
Following IV dosing, tocilizumab undergoes biphasic elimination from the circulation. In RA patients the central volume of distribution was 3.5 L and the peripheral volume of distribution was 2.9 L, resulting in a volume of distribution at steady state of 6.4 L.

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.

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

In paediatric patients with sJIA, the central volume of distribution was 0.94 L and the peripheral volume of distribution was 1.60 L resulting in a volume of distribution at steady state of 2.54 L.

Biotransformation
Not applicable.

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 12.5 mL/h in RA patients, 6.7 mL/h in GCA patients, 5.8 mL/h in paediatric patients with pJIA and 7.1 mL/h in paediatric patients with sJIA. The concentration-dependent nonlinear clearance plays a major role at low tocilizumab concentrations. Once the nonlinear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance. Due to dependence of total clearance on tocilizumab serum concentrations, t1/2 of tocilizumab is also concentration-dependent and can only be calculated at a given serum concentration level.

In RA patients, for intravenous administration, the concentration-dependent apparent $t_{1/2}$ is up to 11 days for 4 mg/kg and 13 days for 8 mg/kg every 4 weeks in patients with RA at steady-state. For subcutaneous administration, the concentration-dependent apparent $t_{1/2}$ is up to 13 days for 162 mg every week and 5 days for 162 mg every other week in patients with RA at steady-state. At high serum concentrations, when total clearance of tocilizumab is dominated by linear clearance, a terminal t1/2 of approximately 21.5 days was derived from the population parameter estimates.

In GCA patients, at steady state, the effective $t_{1/2}$ of tocilizumab 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 week regimen. At high serum concentrations, when total clearance of tocilizumab is dominated by linear clearance, an effective t1/2 of approximately 32 days was derived from the population parameter estimates.

In children with pJIA, the $t_{1/2}$ of tocilizumab is up to 16 days for the two body weight categories (8 mg/kg for BW ≥ 30 kg or 10 mg/kg for BW < 30 kg) during a dosing interval at steady state.

In children with sJIA, the $t_{1/2}$ of tocilizumab is up to 23 days for the two body weight categories (8 mg/kg for body weight ≥ 30 kg or 12 mg/kg for body weight < 30 kg) at week 12.

Pharmacokinetics in Special Populations
Hepatic Impairment: No formal study of the effect of hepatic impairment on the pharmacokinetics of Actemra was conducted.

Renal Impairment: No formal study of the effect of renal impairment on the pharmacokinetics of Actemra was conducted.

Most of the patients in the RA and GCA studies in the 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. Actemra has not been studied in patients with severe renal impairment.

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

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

Other special populations: Population pharmacokinetics in adult RA and GCA patients showed that age, sex and race did not affect the pharmacokinetics of Actemra. No dose adjustment is necessary for these demographic factors.

5.3 Preclinical safety data

Carcinogenicity
A carcinogenicity study of tocilizumab has not been conducted. Proliferating lesions were not observed in a chronic cynomolgus monkey 6-month toxicity study.

Genotoxicity
Standard genotoxicity studies with tocilizumab in both prokaryotic and eukaryotic cells were negative.

Other toxicological information
The non-clinical safety profile of tocilizumab in the cynomolgus monkey does not suggest a difference between IV and SC routes of administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Concentrate for solution for IV infusion
Polysorbate 80, sucrose, dibasic sodium phosphate dodecahydrate, monobasic sodium phosphate dihydrate and water for injections.

Solution for SC injection
Histidine, histidine hydrochloride, polysorbate 80, arginine, arginine hydrochloride, methionine and water for injections.

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

6.3 Shelf life

Concentrate for solution for IV infusion
Unopened vial: 30 months

Diluted product: The prepared infusion solution of Actemra is physically and chemically stable in 0.9% w/v sodium chloride solution at 30ºC for 24 hours. To reduce microbiological hazard, the prepared infusion should be used immediately. If storage is necessary, hold at 2ºC – 8ºC for not more than 24 hours.

Solution for SC injection
24 months.

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

6.4 Special precautions for storage

Concentrate for solution for IV infusion
Store vials at 2 ºC to 8 ºC. (Refrigerate. Do not freeze.) Keep the container in the outer carton in order to protect from light.

Actemra does not contain any antimicrobial agent; therefore care must be taken to ensure the sterility of the prepared solution. Product is for single use in one patient only. Discard any residue.

Do not use after the expiry date (EXP) shown on the pack.

Solution for SC injection
Store the pre-filled syringe at 2°C to 8°C. Refrigerate. Do not freeze. Keep in carton to protect from light and keep dry.

Actemra does not contain any antimicrobial agent. Product is for single use in one patient only. Discard any residue.

The medicine should not be used after the expiry date shown on the pre-filled syringe and the carton.

6.5 Nature and contents of container

Concentrate for solution for IV infusion
Actemra is supplied in preservative-free, non-pyrogenic single-use, clear glass vials.

Actemra is available as:
- Single use vial containing 80 mg of Actemra in 4 mL (20 mg/mL). Packs of 1 and 4* vials.
- Single use vial containing 200 mg of Actemra in 10 mL (20 mg/mL). Packs of 1 and 4* vials.
- Single use vial containing 400 mg of Actemra in 20 mL (20 mg/mL). Packs of 1 and 4* vials.

*Not marketed

Solution for SC injection
Actemra is supplied as a preservative-free, non-pyrogenic solution presented in a ready-to-use, single-use pre-filled syringe with needle safety device. Each syringe contains 162 mg of Actemra in 0.9 mL. Actemra solution for subcutaneous injection comes in packs of 4 syringes.

6.6 Special precautions for disposal
The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

Disposal of syringes/sharps
The following points should be strictly adhered to regarding the use and disposal of the pre-filled syringe:
- Syringes should never be reused
- Place all used syringes into a sharps container (puncture-proof disposable container)
- Keep this container out of the reach of children
- Placing used sharps containers in the household waste should be avoided
- Dispose of the full container according to local requirements or as instructed by your healthcare provider

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

7. MEDICINE SCHEDULE
Prescription Medicine

8. SPONSOR

Roche Products (New Zealand) Limited
PO Box 109113 Newmarket
Auckland 1149
NEW ZEALAND

Medical enquiries: 0800 656 464

9. DATE OF FIRST APPROVAL

Concentrate for solution for IV infusion
23 July 2009

Solution for SC injection
2 April 2015

10. DATE OF REVISION OF THE TEXT

08 April 2019

Summary of Changes Table

Section Changed	Summary of new information
4.4	Inclusion of data relating to hepatotoxicity
4.8	Update to section, *Liver Enzyme Elevations, Rheumatoid Arthritis, Intravenous Administration* with updated data from Study WA25204 (ENTRACTE) Update to Table 2, *Adverse Drug Reactions from post-marketing experience* with inclusion of *Hepatobiliary disorders*