ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 20 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL concentrate contains 20 mg tocilizumab*.

Each vial contains 80 mg of tocilizumab* in 4 mL (20 mg/mL).
Each vial contains 200 mg of tocilizumab* in 10 mL (20 mg/mL).
Each vial contains 400 mg of tocilizumab* in 20 mL (20 mg/mL).

*humanised IgG1 monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipients with known effects
Each 80 mg vial contains 0.10 mmol (2.21 mg) sodium and 2 mg (0.5 mg/mL) polysorbate 80.
Each 200 mg vial contains 0.20 mmol (4.43 mg) sodium and 5 mg (0.5 mg/mL) polysorbate 80.
Each 400 mg vial contains 0.39 mmol (8.85 mg) sodium and 10 mg (0.5 mg/mL) polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to opalescent, colourless to pale yellow solution with a pH of 6.3-6.7 and an osmolality of 172-229 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis (RA)
RoActemra, in combination with methotrexate (MTX), is indicated for:

- the treatment of severe, active and progressive RA in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.
RoActemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with MTX.

Coronavirus disease 2019 (COVID-19)
RoActemra is indicated for the treatment of COVID-19 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

Systemic juvenile idiopathic arthritis (sJIA)
RoActemra is indicated for the treatment of active sJIA in patients 2 years of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and

systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

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

Cytokine release syndrome (CRS)
RoActemra is indicated for the treatment of chimeric antigen receptor (CAR) T cell induced severe or life-threatening CRS in adults and paediatric patients 2 years of age and older.

4.2 Posology and method of administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA, COVID-19, sJIA, pJIA or CRS.

All patients treated with RoActemra must be given the Patient Card.

Posology
RA patients
The recommended posology is 8 mg/kg body weight, given once every four weeks.

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

Doses above 1.2 g have not been evaluated in clinical trials (see section 5.1).

Dose adjustments due to laboratory abnormalities (see section 4.4)

- Liver enzyme abnormalities

Laboratory value	Action
> 1 to 3 × Upper Limit of Normal (ULN)	Modify the dose of the concomitant MTX if appropriate. For persistent increases in this range, reduce tocilizumab dose to 4 mg/kg or interrupt treatment until alanine aminotransferase (ALT) or aspartate aminotransferase (AST) have normalised. Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate.
> 3 to 5 × ULN (confirmed by repeat testing, see section 4.4).	Interrupt tocilizumab dosing until < 3 × ULN and follow recommendations above for > 1 to 3 × ULN. For persistent increases > 3 × ULN, discontinue treatment.
> 5 × ULN	Discontinue treatment.

- Low absolute neutrophil count (ANC)

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

Laboratory Value (cells × 10^9/L)	Action
ANC > 1	Maintain dose.
ANC 0.5 to 1	Interrupt tocilizumab dosing. When ANC increases > 1 × 10^9/ L resume treatment at 4 mg/kg and increase to 8 mg/kg as clinically appropriate.
ANC < 0.5	Discontinue treatment.

- Low platelet count

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

COVID-19 patients
The recommended posology for treatment of COVID-19 is a single 60-minute intravenous infusion of 8 mg/kg body weight in patients who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation, see section 5.1. If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of tocilizumab 8 mg/kg may be administered. The interval between the two infusions must be at least 8 hours.

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

Administration of tocilizumab is not recommended in patients with COVID-19 who have any of the following laboratory abnormalities:

Laboratory test type	Laboratory value	Action
Liver enzyme	> 10 × ULN	Administration of tocilizumab is not recommended
Absolute neutrophil count	< 1 × 10^9/L	
Platelet count	< 50 × 10^3/µL	

Cytokine Release Syndrome (CRS) (adults and paediatrics)
The recommended posology for treatment of CRS given as a 60-minute intravenous infusion is 8 mg/kg in patients weighing greater than or equal to 30 kg or 12 mg/kg in patients weighing less than 30 kg. Tocilizumab can be given alone or in combination with corticosteroids.

If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses of tocilizumab may be administered. The interval between consecutive doses must be at least 8 hours. Doses exceeding 800 mg per infusion are not recommended in CRS patients.

Patients with severe or life-threatening CRS frequently have cytopenias or elevated ALT or AST due to the underlying malignancy, preceding lymphodepleting chemotherapy or the CRS.

Special populations

Elderly

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

Renal impairment

No dose adjustment is required in patients with mild renal impairment. Tocilizumab has not been studied in patients with moderate to severe renal impairment (see section 5.2). Renal function must be monitored closely in these patients.

Hepatic impairment

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

Paediatric population

sJIA patients

The recommended posology in patients above 2 years of age is 8 mg/kg once every 2 weeks in patients weighing greater than or equal to 30 kg or 12 mg/kg once every 2 weeks in patients weighing less than 30 kg. The dose must be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time.

The safety and efficacy of intravenous tocilizumab in children below 2 years of age has not been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Dose interruptions of tocilizumab for the following laboratory abnormalities are recommended in sJIA patients in the tables below. If appropriate, the dose of concomitant MTX and/or other medicinal products should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many co-morbid conditions that may affect laboratory values in sJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.

- Liver enzyme abnormalities

Laboratory Value	Action
> 1 to 3 × ULN	Modify the dose of the concomitant MTX if appropriate. For persistent increases in this range, interrupt tocilizumab until ALT/AST have normalised.
> 3 × ULN to 5 × ULN	Modify the dose of the concomitant MTX if appropriate. Interrupt tocilizumab dosing until < 3 × ULN and follow recommendations above for > 1 to 3 × ULN.
> 5 × ULN	Discontinue tocilizumab. The decision to discontinue treatment in sJIA for a laboratory abnormality must be based on the medical assessment of the individual patient.

- Low absolute neutrophil count (ANC)

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

- Low platelet count

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

There are insufficient clinical data to assess the impact of a tocilizumab dose reduction in sJIA patients who have experienced laboratory abnormalities.

Available data suggest that clinical improvement is observed within 6 weeks of initiation of treatment with tocilizumab. Continued therapy must be carefully reconsidered in a patient exhibiting no improvement within this timeframe.

pJIA patients
The recommended posology in patients above 2 years of age is 8 mg/kg once every 4 weeks in patients weighing greater than or equal to 30 kg or 10 mg/kg once every 4 weeks in patients weighing less than 30 kg. The dose must be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time.

The safety and efficacy of intravenous tocilizumab in children below 2 years of age has not been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

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

- Liver enzyme abnormalities

Laboratory Value	Action
> 1 to 3 × ULN	Modify the dose of the concomitant MTX if appropriate. For persistent increases in this range, interrupt tocilizumab until ALT/AST have normalised.
> 3 × ULN to 5 × ULN	Modify the dose of the concomitant MTX if appropriate. Interrupt tocilizumab dosing until < 3 × ULN and follow recommendations above for > 1 to 3 × ULN.
> 5 × ULN	Discontinue tocilizumab. The decision to discontinue treatment in pJIA for a laboratory abnormality must be based on the medical assessment of the individual patient.

- Low absolute neutrophil count (ANC)

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

- Low platelet count

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

Reduction of tocilizumab dose due to laboratory abnormalities has not been studied in pJIA patients.

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

CRS
Tocilizumab may be used in paediatric patients (2 years of age and older) at the same posology as in adults in CRS. See section 4.2 Posology and method of administration, Cytokine Release Syndrome (CRS) (adults and paediatrics) subsection.

Method of administration
After dilution, this medicinal product should be administered as an intravenous infusion over 1 hour. If signs and symptoms of an infusion-related reaction occur, the infusion needs to be slowed or stopped and appropriate medicinal product/supportive care must be administered immediately (see section 4.4).

RA, sJIA, pJIA, CRS and COVID-19 patients ≥ 30 kg
This medicinal product needs to be diluted to a final volume of 100 mL with sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection using aseptic technique.

For instructions on dilution of the medicinal product before administration, see section 6.6.

sJIA, pJIA and CRS patients < 30 kg
This medicinal product needs to be diluted to a final volume of 50 mL with sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection using aseptic technique.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

Active, severe infections with the exception of COVID-19 (see section 4.4).

4.4 Special warnings and precautions for use

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

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

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

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

Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur during or after therapy with this medicinal product.

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

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

Hypersensitivity reactions
Serious hypersensitivity reactions have been reported in association with infusion of tocilizumab (see section 4.8). Such reactions may be more severe, and potentially fatal in patients who have experienced hypersensitivity reactions during previous infusions even if they have received premedication with steroids and antihistamines. Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during treatment. If an anaphylactic reaction or other serious hypersensitivity / serious infusion-related reaction occurs, administration of tocilizumab must be stopped immediately and treatment should be permanently discontinued.

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

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

Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, have been observed with tocilizumab (see section 4.8). Serious hepatic injury occurred between 2 weeks to more than 5 years after initiation of treatment. Cases of liver failure resulting in liver transplantation have been reported. Patients must be advised to immediately seek medical help if they experience signs and symptoms of hepatic injury.

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

In RA, pJIA and sJIA patients, ALT/AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended modifications,

including tocilizumab discontinuation, based on transaminases levels see section 4.2. For ALT or AST elevations > 3-5 × ULN, confirmed by repeat testing, treatment must be interrupted.

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

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

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

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

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

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

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

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

Malignancy
The risk of malignancy is increased in patients with RA. Immunomodulatory medicinal products may increase the risk of malignancy. The clinical data are insufficient to assess the potential incidence of malignancy following exposure to tocilizumab. Long-term safety evaluations are ongoing.

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

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

Combination with TNF antagonists
There is no experience with the use of tocilizumab with TNF antagonists or other biological treatments for RA, pJIA or sJIA patients. This medicinal product is not recommended for use with other biological agents.

Sodium
After dilution with 0.9% sodium chloride solution, this medicinal product contains 230.6 mg sodium per maximum dose of 800 mg, equivalent to 11.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Polysorbate
This medicine contains 2 mg of polysorbate 80 in each 80 mg vial, 5 mg of polysorbate 80 in each 200 mg vial and 10 mg polysorbate 80 in each 400 mg vial, which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions. Patients' known allergies shall be taken into consideration.

COVID-19 patients
- The efficacy of this medicinal product has not been established in the treatment of COVID-19 patients who do not have elevated CRP levels, see section 5.1.
- This medicinal product must not be administered to COVID-19 patients who are not receiving systemic corticosteroids as an increase in mortality cannot be excluded in this subgroup, see section 5.1.

Infections
In COVID-19 patients, this medicinal product should not be administered if they have any other concurrent severe active infection. Healthcare professionals should exercise caution when considering the use of tocilizumab in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes, and interstitial lung disease) which may predispose patients to infections.

Hepatotoxicity
Patients hospitalised with COVID-19 may have elevated ALT or AST levels. Multi-organ failure with involvement of the liver is recognised as a complication of severe COVID-19. The decision to administer tocilizumab should balance the potential benefit of treating COVID-19 against the potential risks of acute treatment with tocilizumab. In COVID-19 patients with elevated ALT or AST above 10 × ULN, administration of tocilizumab treatment is not recommended. In COVID-19 patients, ALT /AST should be monitored according to current standard clinical practices.

Haematological abnormalities
In COVID-19 patients who develop an ANC < 1×10^9/L or a platelet count < 50×10^3/µL, administration of treatment is not recommended. Neutrophil and platelet counts should be monitored according to current standard clinical practices, see section 4.2.

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

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

Population pharmacokinetic analyses did not detect any effect of MTX, NSAIDs or corticosteroids on tocilizumab clearance.

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

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

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

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

4.6 Fertility, pregnancy and lactation

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

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

RoActemra should not be used during pregnancy unless clearly necessary.

Breast-feeding
It is unknown whether tocilizumab is excreted in human milk. The excretion of tocilizumab in milk has not been studied in animals. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from RoActemra therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

4.7 Effects on ability to drive and use machines

RoActemra has minor influence on the ability to drive and use machines, e.g. dizziness (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
RA, sJIA, pJIA and CRS
The most commonly reported adverse reactions are upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

The most serious adverse reactions are serious infections, complications of diverticulitis, and hypersensitivity reactions.

COVID-19
The most commonly reported adverse reactions are hepatic transaminases increased, constipation, and urinary tract infection.

Tabulated list of adverse reactions
Adverse reactions from clinical trials and/or post-marketing experience with tocilizumab based on spontaneous case reports, literature cases and cases from non-interventional study programs are listed in Table 1 and in Table 2 by MedDRA system organ class (SOC). The corresponding frequency category for each adverse 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), and frequency not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

RA patients

Table 1. List of adverse reactions occurring in patients with RA receiving tocilizumab as monotherapy or in combination with MTX or other DMARDs in the double-blind controlled period or during post-marketing experience

MedDRA SOC	**Frequency categories with preferred terms**				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Infections and infestations	Upper respiratory tract infections	Cellulitis, Pneumonia, Oral herpes simplex, Herpes zoster	Diverticulitis		
Blood and lymphatic system disorders		Leukopenia, Neutropenia, Hypofibrino-genaemia			
Immune system disorders				Anaphylaxis (fatal)[1, 2 ,3]	
Endocrine disorders			Hypothy-roidism		
Metabolism and nutrition disorders	Hypercholeste rolaemia*		Hypertri-glyceridaemia		
Nervous system disorders		Headache, Dizziness			
Eye disorders		Conjunctivitis			
Vascular disorders		Hypertension			
Respiratory , thoracic and mediastinal disorders		Cough, Dyspnoea			

MedDRA SOC	Frequency categories with preferred terms				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Gastroin-testinal disorders		Abdominal pain, Mouth ulceration, Gastritis	Stomatitis, Gastric ulcer		
Hepatobi-liary disorders				Drug-induced liver injury, Hepatitis, Jaundice, :	Hepatic failure
Skin and subcutane-ous tissue disorders		Rash, Pruritus, Urticaria		Stevens-Johnson-Syndrome[3]	
Renal and urinary disorders			Nephroli-thiasis		
General disorders and administra-tion site conditions		Peripheral oedema, Hypersensitiv ity reactions			
Investiga-tions		Hepatic transaminases increased, Weight increased, Total bilirubin increased*			

* Includes elevations collected as part of routine laboratory monitoring (see text below)
[1] See section 4.3
[2] See section 4.4
[3] This adverse reaction was identified through post-marketing surveillance but not observed in controlled clinical trials. The frequency category was estimated as the upper limit of the 95% confidence interval calculated on the basis of the total number of patients exposed to tocilizumab in clinical trials.

Patients with COVID-19
The safety evaluation of this medicinal product in COVID-19 was based on 3 randomised, double-blind, placebo-controlled trials (studies ML42528, WA42380, and WA42511). A total of 974 patients were exposed to tocilizumab in these studies. Collection of safety data from the RECOVERY trial was limited and is not presented here.

The following adverse reactions, listed by MedDRA SOC in Table 2, have been adjudicated from events which occurred in at least 3% of tocilizumab treated patients and more commonly than that in patients on placebo in the pooled safety-evaluable population from clinical trials ML42528, WA42380, and WA42511.

Table 2. List of adverse reactions[1] identified from the pooled safety-evaluable population from tocilizumab clinical trials in COVID-19 patients[2]

MedDRA SOC Class	**Preferred Terms and frequency Common**
Infections and infestations	Urinary tract infection
Metabolism and nutrition disorders	Hypokalaemia
Psychiatric disorders	Anxiety, Insomnia
Vascular disorders	Hypertension
Gastrointestinal disorders	Constipation, Diarrhoea, Nausea
Hepatobiliary disorders	Hepatic transaminases increased

[1] Patients are counted once for each category regardless of the number of reactions
[2] Includes adjudicated reactions reported in studies WA42511, WA42380 and ML42528

Patients with sJIA or pJIA
Adverse reactions in the sJIA and pJIA patients treated with tocilizumab are listed in the Table 3 and presented by MedDRA SOC. The corresponding frequency category for each adverse reaction is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10) or uncommon (≥ 1/1 000 to < 1/100).

Table 3. List of adverse reactions occurring in clinical trial patients with sJIA or pJIA receiving tocilizumab as monotherapy or in combination with MTX.

MedDRA SOC	**Preferrred term (PT)**	**Frequency**		
Infections and Infestations		Very Common	Common	Uncommon
	Upper Respiratory Tract Infections	pJIA, sJIA		
	Nasopharyngitis	pJIA, sJIA		
Nervous system disorders				
	Headache	pJIA	sJIA	
Gastrointestinal Disorders				
	Nausea		pJIA	
	Diarrhoea		pJIA, sJIA	
General disorders and administration site conditions				
	Infusion related reactions		pJIA[1], sJIA[2]	
Investigations				
	Hepatic transaminases increased		pJIA	
	Decrease in neutrophil count	sJIA	pJIA	
	Platelet count decreased		sJIA	pJIA
	Cholesterol increased		sJIA	pJIA

1. Infusion-related reaction events in pJIA patients included but were not limited to headache, nausea and hypotension
2. Infusion-related reaction events in sJIA patients included but were not limited to rash, urticaria, diarrhoea, epigastric discomfort, arthralgia and headache

Description of selected adverse reactions
RA patients
Infections

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

In 6-month controlled clinical trials, the rate of serious infections with tocilizumab 8 mg/kg plus DMARDs was 5.3 events per 100 patient years exposure compared to 3.9 events per 100 patient years exposure in the placebo plus DMARD group. In the monotherapy study, the rate of serious infections was 3.6 events per 100 patient years of exposure in the tocilizumab group and 1.5 events per 100 patient years of exposure in the MTX group.

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

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

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

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

The rate of anaphylactic reactions (occurring in a total of 8/4,009 patients, 0.2%) was several fold higher with the 4 mg/kg dose, compared to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported in a total of 56 out of 4 009 patients (1.4%) treated during the controlled and open label clinical trials. These reactions were generally observed during the second to fifth infusions of tocilizumab (see section 4.4). Fatal anaphylaxis has been reported after marketing authorisation during treatment with tocilizumab (see section 4.4).

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

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

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

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

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

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

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

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

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

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

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

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

COVID-19 patients
Infections
In the pooled safety-evaluable population from trials ML42528, WA42380, and WA42511, the rates of infection/serious infection events were balanced between COVID-19 patients receiving tocilizumab (30.3%/18.6%, n=974) versus placebo (32.1%/22.8%, n=483).

The safety profile observed in the baseline systemic corticosteroids treatment group was consistent with the safety profile of tocilizumab from the overall population presented in Table 2. In this

subgroup, infections and serious infections occurred in 27.8% and 18.1% of patients treated with intravenous tocilizumab and in 30.5% and 22.9% of patients treated with placebo, respectively.

Laboratory abnormalities
The incidence of laboratory abnormalities was generally similar between patients with COVID-19 who received one or two doses of tocilizumab-intravenous compared with those who received placebo in the randomised, double-blind, placebo-controlled trials with few exceptions. Decreases in platelets and neutrophils and elevations of ALT and AST were more frequent among patients receiving tocilizumab-intravenous versus placebo (see section 4.2 and 4.4).

Paediatric population
In general, the adverse reactions in pJIA and sJIA patients were similar in type to those seen in RA patients, see section 4.8.
Description of selected adverse reactions in pJIA patients
The safety profile of intravenous tocilizumab in pJIA has been studied in 188 patients from 2 to 17 years of age. The total patient exposure was 184.4 patient years. The frequency of adverse reactions in pJIA patients can be found in Table 3. The types of adverse reactions in pJIA patients were similar to those seen in RA and sJIA patients. When compared to the adult RA population, events of nasopharyngitis, headache, nausea, and decreased neutrophil count were more frequently reported in the pJIA population. Events of cholesterol increased were less frequently reported in the pJIA population than in the adult RA population.

Infections
The rate of infections in the tocilizumab all exposure population was 163.7 per 100 patient years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was numerically higher in patients weighing < 30 kg treated with 10 mg/kg tocilizumab (12.2 per 100 patient years) compared to patients weighing ≥ 30 kg, treated with 8 mg/kg tocilizumab (4.0 per 100 patient years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing < 30 kg treated with 10 mg/kg tocilizumab (21.4%) compared to patients weighing ≥ 30 kg, treated with 8 mg/kg tocilizumab (7.6%).

Infusion-related reactions
In pJIA patients, infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion. In the tocilizumab all exposure population, 11 patients (5.9%) experienced infusion-related reactions during the infusion and 38 patients (20.2%) experienced an event within 24 hours of an infusion. The most common events occurring during infusion were headache, nausea and hypotension and within 24 hours of infusion were dizziness and hypotension. In general, the adverse reactions observed during or within 24 hours of an infusion were similar in nature to those seen in RA and sJIA patients, see section 4.8.

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

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

Neutrophils
During routine laboratory monitoring in the tocilizumab all exposure population, a decrease in neutrophil count below 1×10^9/L occurred in 3.7% of patients.

Platelets
During routine laboratory monitoring in the tocilizumab all exposure population, 1% of patients had a decrease in platelet count to$\leq 50 \times 10^3$/μL without associated bleeding events.

Hepatic transaminase elevations

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

Lipid parameters
During routine laboratory monitoring in the intravenous tocilizumab study WA19977 3.4% and 10.4% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL at any time during the study treatment, respectively.

Description of selected adverse reactions in sJIA patients
The safety profile of intravenous tocilizumab in sJIA has been studied in 112 patients from 2 to 17 years of age. In the 12 week double-blind, controlled phase, 75 patients received treatment with tocilizumab (8 mg/kg or 12 mg/kg based upon body weight). After 12 weeks or at the time of switching from placebo to tocilizumab, due to disease worsening, patients were treated in the open label extension phase.

In general, the adverse reactions in sJIA patients were similar in type to those seen in RA patients. The frequency of adverse reactions in sJIA patients can be found in Table 3. When compared to the adult RA population, patients with sJIA experienced a higher frequency of nasopharyngitis, decrease in neutrophil counts, hepatic transaminases increased, and diarrhoea. Events of cholesterol increased were less frequently reported in the sJIA population than in the adult RA population.

Infections
In the 12 week controlled phase, the rate of all infections in the intravenous tocilizumab group was 344.7 per 100 patient years and 287.0 per 100 patient years in the placebo group. In the open label extension phase (Part II), the overall rate of infections remained similar at 306.6 per 100 patient years.

In the 12 week controlled phase, the rate of serious infections in the intravenous tocilizumab group was 11.5 per 100 patient years. At one year in the open label extension phase the overall rate of serious infections remained stable at 11.3 per 100 patient years. Reported serious infections were similar to those seen in RA patients with the addition of varicella and otitis media.

Infusion-related reactions
Infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion. In the 12 week controlled phase, 4% of patients from the tocilizumab group experienced events occurring during infusion. One event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment.

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

Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation, were reported in 1 out of 112 patients (< 1%) treated with tocilizumab during the controlled and up to and including the open label clinical trial.

Immunogenicity
All 112 patients were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti-tocilizumab antibodies with one of these patients having a hypersensitivity reaction leading to withdrawal. The incidence of anti-tocilizumab antibody formation might be underestimated because of interference of tocilizumab with the assay and higher tocilizumab concentration observed in children compared to adults.

Neutrophils
During routine laboratory monitoring in the 12 week controlled phase, a decrease in neutrophil counts below 1×10^9/L occurred in 7% of patients in the tocilizumab group, and no decreases in the placebo group.

In the open label extension phase, decreases in neutrophil counts below 1×10^9/L, occurred in 15% of the tocilizumab group.

Platelets
During routine laboratory monitoring in the 12 week controlled phase, 3% of patients in the placebo group and 1% in the tocilizumab group had a decrease in platelet count to $\leq 100 \times 10^3$/µL.

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

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

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

Immunoglobulin G
IgG levels decrease during therapy. A decrease to the lower limit of normal occurred in 15 patients at some point in the study.

Lipid parameters
During routine laboratory monitoring in the 12 week controlled phase (study WA18221), 13.4% and 33.3% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL at any time during study treatment, respectively.

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

CRS patients
The safety of tocilizumab in CRS has been evaluated in a retrospective analysis of data from clinical trials, where 51 patients were treated with intravenous tocilizumab 8 mg/kg (12 mg/kg for patients less than 30 kg) with or without additional high-dose corticosteroids for severe or life-threatening CAR T cell-induced CRS. A median of 1 dose of tocilizumab (range, 1-4 doses) was administered.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Pharmacodynamic effects
In clinical trials with RA patients treated with tocilizumab, rapid decreases in CRP, erythrocyte sedimentation rate (ESR), serum amyloid A (SAA) and fibrinogen were observed. Consistent with the effect on acute phase reactants, treatment with tocilizumab was associated with reduction in platelet count within the normal range. Increases in haemoglobin levels were observed, through tocilizumab decreasing the IL-6 driven effects on hepcidin production to increase iron availability. In treated patients, decreases in the levels of CRP to within normal ranges were seen as early as week 2, with decreases maintained while on treatment.

In healthy subjects administered tocilizumab in doses from 2 to 28 mg/kg, absolute neutrophil counts decreased to their lowest 3 to 5 days following administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. Rheumatoid arthritis patients demonstrated a similar pattern of absolute neutrophil counts following tocilizumab administration (see section 4.8).

In COVID-19 patients with one dose of tocilizumab 8 mg/kg administered intravenously, decreases in the levels of CRP to within normal ranges were seen as early as day 7.

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

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

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

Study II, a two-year study with planned analyses at week 24, week 52 and week 104, evaluated 1,196 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of tocilizumab or placebo were given every four weeks as blinded therapy for 52 weeks in combination with stable MTX (10 mg to 25 mg weekly). After week 52, all patients could receive open-label treatment with tocilizumab 8 mg/kg. Of the patients who completed the study who were originally randomised to placebo + MTX, 86% received open-label tocilizumab 8 mg/kg in year 2. The primary endpoint at week 24 was the proportion of patients who achieved an ACR 20 response. At week 52 and week 104 the co-primary endpoints were prevention of joint damage and improvement in physical function.

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

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

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

Clinical response
In all trials, patients treated with tocilizumab 8 mg/kg had statistically significant higher ACR 20, 50, 70 response rates at 6 months compared to control (Table 4). In study I, superiority of tocilizumab 8 mg/kg was demonstrated against the active comparator MTX.

The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race, number of prior treatments or disease status. Time to onset was rapid (as early as week 2) and the magnitude of response continued to improve with duration of treatment. Continued durable responses were seen for over 3 years in the open label extension trials I-V.

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

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

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

Table 4. ACR responses in placebo-/MTX-/DMARDs-controlled trials (% patients)

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

ACR - American College of Rheumatology (ACR) criteria
TCZ - Tocilizumab
MTX - Methotrexate
PBO - Placebo
DMARD - Disease modifying anti-rheumatic drug
** - $p < 0.01$, TCZ vs. PBO + MTX/DMARD
*** - $p < 0.0001$, TCZ vs. PBO + MTX/DMARD

Major clinical response
After 2 years of treatment with tocilizumab plus MTX, 14% of patients achieved a major clinical response (maintenance of an ACR 70 response for 24 weeks or more).

Radiographic response
In Study II, in patients with an inadequate response to MTX, inhibition of structural joint damage was assessed radiographically and expressed as change in modified Sharp score and its components, the erosion score and joint space narrowing score. Inhibition of joint structural damage was shown with significantly less radiographic progression in patients receiving tocilizumab compared to control (Table 5).

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

Table 5. Radiographic mean changes over 52 weeks in Study II

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

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

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

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

Haemoglobin levels
Statistically significant improvements in haemoglobin levels were observed with tocilizumab compared with DMARDs ($p < 0.0001$) at week 24. Mean haemoglobin levels increased by week 2 and remained within normal range through to week 24.

Tocilizumab versus adalimumab in monotherapy
Study VI (WA19924), a 24-week double-blinded study that compared tocilizumab monotherapy with adalimumab monotherapy, evaluated 326 patients with RA who were intolerant of MTX or where continued treatment with MTX was considered inappropriate (including MTX inadequate responders). Patients in the tocilizumab arm received an intravenous infusion of tocilizumab (8 mg/kg) every 4 weeks (q4w) and a subcutaneous placebo injection every 2 weeks (q2w). Patients in the adalimumab arm received an adalimumab subcutaneous injection (40 mg) q2w plus an intravenous placebo infusion q4w. A statistically significant superior treatment effect was seen in favour of tocilizumab over adalimumab in control of disease activity from baseline to week 24 for the primary endpoint of change in DAS28 and for all secondary endpoints (Table 6).

Table 6. Efficacy results for Study VI (WA19924)

	ADA + Placebo (IV) N = 162	TCZ + Placebo (SC) N = 163	p-value[(a)]
Primary endpoint - mean change from baseline at week 24			
DAS28 (adjusted mean)	-1.8	-3.3	
Difference in adjusted mean (95% CI)	-1.5 (-1.8, -1.1)		< 0.0001
Secondary endpoints - percentage of responders at week 24 [(b)]			
DAS28 < 2.6, n (%)	17 (10.5)	65 (39.9)	< 0.0001
DAS28 ≤ 3.2, n (%)	32 (19.8)	84 (51.5)	< 0.0001
ACR 20 response, n (%)	80 (49.4)	106 (65.0)	0.0038
ACR 50 response, n (%)	45 (27.8)	77 (47.2)	0.0002
ACR 70 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
IV = intravenous
SC = subcutaneous
TCZ = tocilizumab
ADA = adalimumab

The overall clinical adverse event profile was similar between tocilizumab and adalimumab. The proportion of patients with serious adverse events was balanced between the treatment groups (tocilizumab 11.7% vs. adalimumab 9.9%). The types of adverse reactions in the tocilizumab arm were consistent with the known safety profile of tocilizumab and adverse reactions were reported at a similar frequency compared with Table 1. A higher incidence of infections and infestations was reported in the tocilizumab arm (48% vs. 42%), with no difference in the incidence of serious infections (3.1%). Both study treatments induced the same pattern of changes in laboratory safety parameters (decreases in neutrophil and platelet counts, increases in ALT, AST and lipids), however, the magnitude of change and the frequency of marked abnormalities was higher with tocilizumab compared with adalimumab. Four (2.5%) patients in the tocilizumab arm and two (1.2%) patients in the adalimumab arm experienced CTC grade 3 or 4 neutrophil count decreases. Eleven (6.8%) patients in the tocilizumab arm and five (3.1%) patients in the adalimumab arm experienced ALT increases of CTC grade 2 or higher. The mean LDL increase from baseline was 0.64 mmol/L (25 mg/dL) for patients in the tocilizumab arm and 0.19 mmol/L (7 mg/dL) for patients in the adalimumab arm. The safety observed in the tocilizumab arm was consistent with the known safety profile of tocilizumab and no new or unexpected adverse reactions were observed (see Table 1).

MTX naïve, early RA
Study VII (WA19926), a 2-year study with the planned primary analysis at week 52 evaluated 1162 MTX-naïve adult patients with moderate to severe, active early RA (mean disease duration ≤ 6 months). Approximately 20% of patients had received prior treatment with DMARDs other than MTX. This study evaluated the efficacy of intravenous tocilizumab 4 or 8 mg/kg every 4 weeks/MTX combination therapy, intravenous tocilizumab 8 mg/kg monotherapy and MTX monotherapy in reducing the signs and symptoms and rate of progression of joint damage for 104 weeks. The primary endpoint was the proportion of patients achieving DAS28 remission (DAS28 < 2.6) at week 24. A significantly higher proportion of patients in the tocilizumab 8 mg/kg + MTX and tocilizumab monotherapy groups met the primary endpoint compared with MTX alone. The tocilizumab 8 mg/kg + MTX group also showed statistically significant results across the key secondary endpoints. Numerically greater responses compared with MTX alone were observed in the tocilizumab 8 mg/kg monotherapy group in all secondary endpoints, including radiographic endpoints. In this study, ACR/EULAR remission (Boolean and Index) were also analysed as pre-specified exploratory endpoints, with higher responses observed in the tocilizumab groups. The results from study VII are shown in Table 7.

Table 7. Efficacy Results for Study VII (WA19926) on MTX-naïve, early RA patients

			TCZ 8 mg/kg + MTX N=290	TCZ 8 mg/kg + placebo N=292	TCZ 4 mg/kg + MTX N=288	Placebo + MTX N=287
Primary endpoint						
DAS28 Remission						
week 24	n (%)		130 (44.8)***	113 (38.7)***	92 (31.9)	43 (15.0)
Key secondary endpoints						
DAS 28 remission						
week 52	n (%)		142 (49.0)***	115 (39.4)	98 (34.0)	56 (19.5)
ACR						
week 24	ACR 20, n (%)		216 (74.5)*	205 (70.2)	212 (73.6)	187 (65.2)
		ACR 50, n (%)	165 (56.9)**	139 (47.6)	138 (47.9)	124 (43.2)
		ACR 70, n (%)	112 (38.6)**	88 (30.1)	100 (34.7)	73 (25.4)
week 52	ACR 20, n (%)		195 (67.2)*	184 (63.0)	181 (62.8)	164 (57.1)
		ACR 50, n (%)	162 (55.9)**	144 (49.3)	151 (52.4)	117 (40.8)
		ACR 70, n (%)	125 (43.1)**	105 (36.0)	107 (37.2)	83 (28.9)
HAQ-DI (adjusted mean change from baseline)						
week 52			-0.81*	-0.67	-0.75	-0.64
Radiographic endpoints (mean change from baseline)						
week 52	mTSS		0.08***	0.26	0.42	1.14
		Erosion Score	0.05**	0.15	0.25	0.63
		JSN	0.03	0.11	0.17	0.51
		Radiographic Non-Progression n (%) (change from baseline in mTSS of ≤ 0)	226 (83)‡	226 (82)‡	211 (79)	194 (73)
Exploratory endpoints						
week 24: ACR/EULAR Boolean Remission, n (%)			47 (18.4) ‡	38 (14.2)	43 (16.7) ‡	25 (10.0)
		ACR/EULAR Index Remission, n (%)	73 (28.5) ‡	60 (22.6)	58 (22.6)	41 (16.4)
week 52: ACR/EULAR Boolean Remission, n (%)			59 (25.7) ‡	43 (18.7)	48 (21.1)	34 (15.5)
		ACR/EULAR Index Remission, n (%)	83 (36.1) ‡	69 (30.0)	66 (29.3)	49 (22.4)

mTSS - modified Total Sharp Score
JSN - Joint space narrowing
TCZ – tocilizumab
MTX – methotrexate
ACR - American College of Rheumatology (ACR) criteria
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)

COVID-19

Clinical efficacy

RECOVERY (randomised evaluation of COVID-19 therapy) collaborative group study in hospitalised adults diagnosed with COVID-19

RECOVERY was a large, randomised, controlled, open-label, multi-centre platform study conducted in the United Kingdom to evaluate the efficacy and safety of potential treatments in hospitalised adult patients with severe COVID-19. All eligible patients received usual care and underwent an initial (main) randomisation. Eligible patients for the trial had clinically suspected or laboratory-confirmed SARS-CoV-2 infection and no medical contraindications to any of the treatments. Patients with clinical evidence of progressive COVID-19 (defined as oxygen saturation < 92% on room air or receiving oxygen therapy, and CRP ≥ 75 mg/L) qualified for a second randomisation to receive either intravenous tocilizumab or usual care alone.

Efficacy analyses were performed in the intent-to-treat (ITT) population comprising 4116 patients who were randomised with 2022 patients in the tocilizumab + usual care arm and 2094 patients in the usual care alone arm. The baseline demographic and disease characteristics of the ITT population were well balanced across treatment arms. The mean age of participants was 63.6 years (standard deviation [SD] 13.6 years). The majority of patients were male (67%) and White (76%). The median (range) level of CRP was 143 mg/L (75-982).

At baseline, 0.2% (n=9) of patients were not on supplemental oxygen, 45% of patients required low flow oxygen, 41% of patients required non-invasive ventilation or high-flow oxygen and 14% of patients required invasive mechanical ventilation; 82% were reported receiving systemic corticosteroids (defined as patients who initiated treatment with systemic corticosteroids either prior to or at the time of randomisation). The most common comorbidities were diabetes (28.4%), heart disease (22.6%) and chronic lung disease (23.3%).

The primary outcome was time to death through Day 28. The hazard ratio comparing the tocilizumab + usual care arm to the usual care alone arm was 0.85 (95% CI: 0.76 to 0.94), a statistically significant result (p=0.0028). The probabilities of dying by Day 28 were estimated to be 30.7% and 34.9% in the tocilizumab and usual care arms, respectively. The risk difference was estimated to be -4.1% (95% CI: -7.0% to -1.3%), consistent with the primary analysis. The hazard ratio among the pre-specified subgroup of patients receiving systemic corticosteroids at baseline was 0.79 (95% CI: 0.70 to 0.89), and for the pre-specified subgroup not receiving systemic corticosteroids at baseline was 1.16 (95% CI: 0.91 to 1.48).

The median time to hospital discharge was 19 days in the tocilizumab+ usual care arm and > 28 days in the usual care arm (hazard ratio [95% CI]=1.22 [1.12 to 1.33]).

Among patients not requiring invasive mechanical ventilation at baseline, the proportion of patients who required mechanical ventilation or died by Day 28 was 35% (619/1754) in the tocilizumab + usual care arm and 42% (754/1800) in the usual care alone arm (risk ratio [95% CI] = 0.84, [0.77 to 0.92] p < 0.0001).

Paediatric population with sJIA

Clinical efficacy

The efficacy of tocilizumab for the treatment of active sJIA was assessed in a 12 week randomised, double-blind, placebo-controlled, parallel group, two arm study. Patients included in the trial had a total disease duration of at least 6 months and active disease but were not experiencing an acute flare requiring corticosteroid doses of more than 0.5 mg/kg prednisone equivalent. Efficacy for the treatment of macrophage activation syndrome (MAS) has not been investigated.

Patients (treated with or without MTX) were randomised (tocilizumab:placebo = 2:1) to one of two treatment groups, 75 patients received tocilizumab infusions every two weeks, either 8 mg/kg for patients ≥ 30 kg or 12 mg/kg for patients < 30 kg and 37 patients were assigned to receiving placebo infusions every two weeks. Corticosteroid tapering was permitted from week six for patients who achieved a JIA ACR 70 response. After 12 weeks or at the time of escape, due to disease worsening, patients were treated in the open label phase at weight appropriate dosing.

Clinical response
The primary endpoint was the proportion of patients with at least 30% improvement in the JIA ACR core set (JIA ACR 30 response) at week 12 and absence of fever (no temperature recording ≥ 37.5 °C in the preceding 7 days). Eighty five percent (64/75) of tocilizumab treated patients and 24.3% (9/37) of placebo treated patients achieved this endpoint. These proportions were highly significantly different ($p < 0.0001$).

The percent of patients achieving JIA ACR 30, 50, 70 and 90 responses are shown in Table 8.

Table 8. JIA ACR response rates at week 12 (% patients)

Response rate	**Tocilizumab N = 75**	**Placebo N = 37**
JIA ACR 30	90.7%[1]	24.3%
JIA ACR 50	85.3%[1]	10.8%
JIA ACR 70	70.7%[1]	8.1%
JIA ACR 90	37.3%[1]	5.4%

[1] $p < 0.0001$, tocilizumab vs. placebo

Systemic effects
In the tocilizumab treated patients, 85% who had fever due to sJIA at baseline were free of fever (no temperature recording ≥ 37.5 °C in the preceding 14 days) at week 12 versus 21% of placebo patients ($p < 0.0001$).

The adjusted mean change in the pain VAS after 12 weeks of tocilizumab treatment was a reduction of 41 points on a scale of 0 - 100 compared to a reduction of 1 for placebo patients ($p < 0.0001$).

Corticosteroid tapering
Patients achieving a JIA ACR 70 response were permitted corticosteroid dose reduction. Seventeen (24%) tocilizumab treated patients versus 1 (3%) placebo patient were able to reduce their dose of corticosteroid by at least 20% without experiencing a subsequent JIA ACR 30 flare or occurrence of systemic symptoms to week 12 ($p=0.028$). Reductions in corticosteroids continued, with 44 patients off oral corticosteroids at week 44, while maintaining JIA ACR responses.

Health related and quality of life outcomes
At week 12, the proportion of tocilizumab treated patients showing a minimally clinically important improvement in the Childhood Health Assessment Questionnaire – Disability Index (defined as an individual total score decrease of ≥ 0.13) was significantly higher than in placebo treated patients, 77% versus 19% ($p < 0.0001$).

Laboratory parameters
Fifty out of seventy five (67%) tocilizumab treated patients had a haemoglobin < LLN at baseline. Forty (80%) of these patients had an increase in their haemoglobin to within the normal range at week 12, in comparison to 2 out of 29 (7%) of placebo treated patients with haemoglobin < LLN at baseline ($p < 0.0001$).

Paediatric population with pJIA

Clinical efficacy

The efficacy of tocilizumab was assessed in a three-part study WA19977 including an open-label extension in children with active pJIA. Part I consisted of a 16-week active tocilizumab treatment lead-in period (n=188) followed by Part II, a 24-week randomised double-blind placebo-controlled withdrawal period (n=163), followed by Part III, a 64-week open-label period. In Part 1, eligible patients ≥ 30 kg received tocilizumab at 8 mg/kg intravenous every 4 weeks for 4 doses. Patients < 30 kg were randomised 1:1 to receive either tocilizumab 8 mg/kg or 10 mg/kg intravenous every 4 weeks for 4 doses. Patients who completed Part I of the study and achieved at least a JIA ACR 30 response at week 16 compared to baseline were eligible to enter the blinded withdrawal period (Part II) of the study. In Part II, patients were randomised to tocilizumab (same dose received in Part I) or placebo in a 1:1 ratio, stratified by concurrent MTX use and concurrent corticosteroid use. Each patient continued in Part II of the study until week 40 or until the patient satisfied JIA ACR 30 flare criteria (relative to week 16) and qualified for escape to tocilizumab therapy (same dose received in Part I).

Clinical response

The primary endpoint was the proportion of patients with a JIA ACR 30 flare at week 40 relative to week 16. Forty eight percent (48.1%, 39/81) of the patients treated with placebo flared compared with 25.6% (21/82) of tocilizumab treated patients. These proportions were statistically significantly different (p=0.0024).

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

During the withdrawal phase (Part II), the percentage of patients achieving JIA ACR 30, 50, and 70 responses at week 40 relative to baseline are shown in Table 9. In this statistical analysis, patients who flared (and escaped to tocilizumab) during Part II or who withdrew, were classified as non-responders. An additional analyses of JIA ACR responses, considering observed data at week 40, regardless of flare status, showed that by week 40, 95.1% of patients who had received continuous tocilizumab therapy, had achieved JIA ACR 30 or higher.

Table 9. JIA ACR response rates at week 40 relative to baseline (percentage of patients)

Response rate	Tocilizumab N=82	Placebo N=81
ACR 30	74.4%*	54.3%*
ACR 50	73.2%*	51.9%*
ACR 70	64.6%*	42.0%*

* p < 0.01, tocilizumab vs. placebo

The number of active joints was significantly reduced compared to baseline in patients receiving tocilizumab compared to placebo (adjusted mean changes of -14.3 vs -11.4, p=0.0435). The physician's global assessment of disease activity, as measured on a 0-100 mm scale, showed a greater reduction in disease activity for tocilizumab compared to placebo (adjusted mean changes of -45.2 mm vs -35.2 mm, p=0.0031).

The adjusted mean change in the pain VAS after 40 weeks of tocilizumab treatment was 32.4 mm on a 0-100 mm scale compared to a reduction of 22.3 mm for placebo patients (highly statistically significant; p=0.0076).

The ACR response rates were numerically lower for patients with prior biologic treatment as shown in Table 10 below.

Table 10. Number and proportion of patients with a JIA ACR 30 flare and proportion of patients with JIA ACR 30/50/70/90 responses at week 40, by previous biologic use (ITT Population - Study Part II)

	Placebo		**All TCZ**	
Biologic use	**Yes (N = 23)**	**No (N = 58)**	**Yes (N = 27)**	**No (N = 55)**
JIA ACR 30 Flare	18 (78.3)	21 (36.2)	12 (44.4)	9 (16.4)
JIA ACR 30 Response	6 (26.1)	38 (65.5)	15 (55.6)	46 (83.6)
JIA ACR 50 Response	5 (21.7)	37 (63.8)	14 (51.9)	46 (83.6)
JIA ACR 70 Response	2 (8.7)	32 (55.2)	13 (48.1)	40 (72.7)
JIA ACR 90 Response	2 (8.7)	17 (29.3)	5 (18.5)	32 (58.2)

TCZ = tocilizumab

Patients randomised to tocilizumab had fewer ACR 30 flares and higher overall ACR responses than patients receiving placebo regardless of a history of prior biologic use.

CRS

The efficacy of tocilizumab for the treatment of CRS was assessed in a retrospective analysis of data from clinical trials of CAR T-cell therapies (tisagenlecleucel and axicabtagene ciloleucel) for haematological malignancies. Evaluable patients had been treated with tocilizumab 8 mg/kg. (12 mg/kg for patients < 30 kg) with or without additional high-dose corticosteroids for severe or life-threatening CRS; only the first episode of CRS was included in the analysis. The efficacy population for the tisagenlecleucel cohort included 28 males and 23 females (total 51 patients) of median age 17 years (range, 3–68 years). The median time from start of CRS to first dose of tocilizumab was 3 days (range, 0–18 days). Resolution of CRS was defined as lack of fever and off vasopressors for at least 24 hours. Patients were considered responders if CRS resolved within 14 days of the first dose of tocilizumab, if no more than 2 doses were needed, and no medicinal products other than tocilizumab and corticosteroids were used for treatment. Thirty-nine patients (76.5%; 95% CI: 62.5%–87.2%) achieved a response. In an independent cohort of 15 patients (range: 9–75 years old) with axicabtagene ciloleucel-induced CRS, 53% responded.

The European Medicines Agency has waived the obligation to submit the results of studies with tocilizumab in all subsets of the paediatric population in treatment of cytokine release syndrome associated with CAR T-cell therapy.

COVID-19

The European Medicines Agency has deferred the obligation to submit the results of studies with tocilizumab in one or more subsets of the paediatric population in the treatment of COVID-19.

5.2 Pharmacokinetic properties

RA patients

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 3552 RA patients treated with a one-hour infusion of 4 or 8 mg/kg tocilizumab every 4 weeks for 24 weeks or with 162 mg tocilizumab given subcutaneously either once a week or every other week for 24 weeks.

The following parameters (predicted mean ± SD) were estimated for a dose of 8 mg/kg tocilizumab given every 4 weeks: steady-state area under curve (AUC) = 38 000 ± 13 000 h µg/mL, trough concentration (C_{min}) = 15.9 ± 13.1 µg/mL and maximum concentration (C_{max}) = 182 ± 50.4 µg/mL, and the accumulation ratios for AUC and C_{max} were small, 1.32 and 1.09, respectively. The accumulation ratio was higher for C_{min} (2.49), which was expected based on the non-linear clearance contribution at lower concentrations. Steady-state was reached following the first administration for C_{max} and after 8 and 20 weeks for AUC and C_{min}, respectively. Tocilizumab AUC, C_{min} and C_{max} increased with increase of body weight. At body weight ≥ 100 kg, the predicted mean (± SD)

steady-state AUC, C_{min} and C_{max} of tocilizumab were 50000 ± 16800 µg•h/mL, 24.4 ± 17.5 µg/mL, and 226 ± 50.3 µg/mL, respectively, which are higher than mean exposure values for the patient population (i.e. all body weights) reported above. The dose-response curve for tocilizumab flattens at higher exposure, resulting in smaller efficacy gains for each incremental increase in tocilizumab concentration such that clinically meaningful increases in efficacy were not demonstrated in patients treated with > 800 mg of tocilizumab. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended (see section 4.2).

COVID-19 patients

The pharmacokinetics of tocilizumab was characterised using a population pharmacokinetic analysis of a database composed of 380 adult COVID-19 patients in Study WA42380 (COVACTA) and Study CA42481 (MARIPOSA) that treated with a single infusion of 8 mg/kg tocilizumab or two infusions separated by at least 8 hours. The following parameters (predicted mean ± SD) were estimated for a dose of 8 mg/kg tocilizumab: area under curve over 28 days (AUC_{0-28}) = 18312 (5184) hour•µg/mL, concentration at Day 28 (Cday28) = 0.934 (1.93) µg/mL and maximum concentration (C_{max}) = 154 (34.9) µg/mL. The AUC_{0-28}, C_{day28} and C_{max}, following two doses of 8 mg/kg tocilizumab separated by 8 hours, were also estimated (predicted mean ± SD): 42240 (11520) hour•µg/mL and 8.94 (8.5) µg/mL, and 296 (64.7) µg/mL respectively.

Distribution

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

In COVID-19 adult patients, the central volume of distribution was 4.52 L, the peripheral volume of distribution was 4.23 L, resulting in a volume of distribution of 8.75 L.

Elimination

Following intravenous administration, tocilizumab undergoes a dual elimination from the circulation, one following a linear clearance and one following a concentration-dependent non-linear clearance. In RA patients, the linear clearance was 9.5 mL/h. In COVID-19 adult patients, the linear clearance was 17.6 mL/h in patients with baseline ordinal scale category 3 (OS 3, patients requiring supplemental oxygen), 22.5 mL/h in patients with baseline OS 4 (patients requiring high-flow oxygen or non-invasive ventilation), 29 mL/h in patients with baseline OS 5 (patients requiring mechanical ventilation), and 35.4 mL/h in patients with baseline OS 6 (patients requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support). The concentration-dependent non-linear clearance plays a major role at low tocilizumab concentrations. Once the non-linear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.

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

In COVID-19 patients, serum concentrations were below the limit of quantification after 35 days on average following one infusion of tocilizumab intravenous 8 mg/kg.

Linearity

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

Special populations

Renal impairment

No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab has been conducted. Most of the patients in the population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (creatinine clearance based on Cockcroft-Gault < 80 mL/min and ≥ 50 mL/min) did not impact the pharmacokinetics of tocilizumab.

Hepatic impairment

No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab has been conducted.

Age, gender and ethnicity

Population pharmacokinetic analyses in RA and COVID-19 patients, showed that age, gender and ethnic origin did not affect the pharmacokinetics of tocilizumab.

Results of the population PK analysis for COVID-19 patients confirmed that body weight and disease severity are both covariates which have an appreciable impact on the linear clearance of tocilizumab.

sJIA Patients

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 140 sJIA patients treated with 8 mg/kg intravenous every 2 weeks (patients with a body weight ≥ 30 kg) 12 mg/kg intravenous every 2 weeks (patients with a body weight < 30 kg), 162 mg subcutaneous every week (patients weighing ≥ 30 kg), 162 mg subcutaneous every 10 days or every 2 weeks (patients weighing below 30 kg).

Table 11. Predicted mean ± SD PK parameters at steady-state after intravenous dosing in sJIA

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

*τ = 2 weeks for intravenous regimens

After intravenous dosing, approximately 90% of the steady-state was reached by week 8 for both the 12 mg/kg (body weight < 30 kg) and 8 mg/kg Q2W (body weight ≥ 30 kg) regimens.

In sJIA patients, the central volume of distribution was 1.87 L and the peripheral volume of distribution was 2.14 L resulting in a volume of distribution at a steady-state of 4.01 L. The linear clearance estimated as a parameter in the population pharmacokinetic analysis, was 5.7 mL/h.

The half-life of tocilizumab in sJIA patients is up to 16 days for the two body weight categories (8 mg/kg for body weight ≥ 30 kg or 12 mg/kg for body weight < 30 kg) at week 12.

pJIA patients

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

Table 12. Predicted mean ± SD PK parameters at steady-state after intravenous dosing in pJIA

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

*τ = 4 weeks for intravenous regimens

After intravenous dosing, approximately 90% of the steady-state was reached by week 12 for the 10 mg/kg (body weight < 30 kg), and by week 16 for the 8 mg/kg (body weight ≥ 30 kg) dose.

The half-life of tocilizumab in pJIA patients is up to 16 days for the two body weight categories (8 mg/kg for body weight ≥ 30 kg or 10 mg/kg for body weight < 30 kg) during a dosing interval at steady-state.

5.3 Preclinical safety data

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Polysorbate 80 (E 433)
Disodium phosphate dodecahydrate (for pH-adjustment)
Sodium dihydrogen phosphate dihydrate (for pH-adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
3 years

Diluted product
After dilution, the prepared solution for infusion is physically and chemically stable in sodium chloride 9 mg/mL (0.9%) solution for injection. It can be stored for 24 hours at 30 ºC and for up to 2 weeks in a refrigerator at 2 °C - 8 °C.

From a microbiological point of view, the prepared solution for infusion must be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C - 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

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

For storage conditions after dilution of the medicinal product see section 6.3.

6.5 Nature and contents of container

RoActemra is supplied in a vial (type I glass) with a stopper (butyl rubber) containing 4 mL, 10 mL or 20 mL concentrate. Pack sizes of 1 and 4 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for dilution prior to administration
Parenteral medicinal products must be inspected visually for particulate matter or discolouration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted. Use a sterile needle and syringe to prepare the product.

Adult RA, CRS (≥ 30 kg) and COVID-19 patients
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 100 mL infusion bag, equal to the volume of concentrate required for the patients dose, under aseptic conditions. The required amount of concentrate (0.4 mL/kg) should be withdrawn from the vial

and placed in the 100 mL infusion bag. This should be a final volume of 100 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

Paediatric population
sJIA, pJIA and CRS patients ≥ 30 kg
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 100 mL infusion bag, equal to the volume of concentrate required for the patients dose, under aseptic conditions. The required amount of concentrate (**0.4 mL/kg**) should be withdrawn from the vial and placed in the 100 mL infusion bag. This should be a final volume of 100 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

sJIA and CRS patients < 30 kg
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 50 mL infusion bag, equal to the volume of concentrate required for the patients dose, under aseptic conditions. The required amount of concentrate (**0.6 mL/kg**) should be withdrawn from the vial and placed in the 50 mL infusion bag. This should be a final volume of 50 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

pJIA patients < 30 kg
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 50 mL infusion bag, equal to the volume of concentrate required for the patients dose, under aseptic conditions. The required amount of concentrate (**0.5 mL/kg**) should be withdrawn from the vial and placed in the 50 mL infusion bag. This should be a final volume of 50 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

When diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, RoActemra is compatible with intravenous infusion bags composed of polyvinyl chloride (PVC), polyethylene (PE), polypropylene (PP).

RoActemra is for single-use only.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/08/492/001
EU/1/08/492/002
EU/1/08/492/003
EU/1/08/492/004
EU/1/08/492/005
EU/1/08/492/006

9. DATE OF FIRST AUTHORISATION/DATE OF LATEST RENEWAL

Date of first authorisation: 16 January 2009
Date of last renewal: 25 September 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 162 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Tocilizumab is a recombinant humanised, anti-human monoclonal antibody of the immunoglobulin G1 (IgG1) sub-class.

Excipient with known effects
Each 162 mg/0.9 mL syringe contains 0.18 mg (0.2 mg/mL) polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

A colourless to slightly yellowish solution with a pH of 5.5-6.5 and an osmolality of 200-372 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis (RA)
RoActemra, in combination with methotrexate (MTX), is indicated for

- the treatment of severe, active and progressive RA in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

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

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

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

Giant cell arteritis (GCA)
RoActemra is indicated for the treatment of GCA in adult patients.

4.2 Posology and method of administration

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

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

All patients treated with RoActemra must be given the Patient Card.

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

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

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

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

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

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

RA and GCA patients
Dose adjustments due to laboratory abnormalities (see section 4.4).

- Liver enzyme abnormalities

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

- Low absolute neutrophil count (ANC)

In patients not previously treated with tocilizumab, initiation is not recommended in patients with an ANC below 2×10^9/L

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

- Low platelet count

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

RA and GCA
Missed dose

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

Special populations

Elderly

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

Renal impairment

No dose adjustment is required in patients with mild or moderate renal impairment. Tocilizumab has not been studied in patients with severe renal impairment (see section 5.2). Renal function must be monitored closely in these patients.

Hepatic impairment

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

Paediatric population

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

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

sJIA patients

The recommended posology in patients above 1 year of age is subcutaneous 162 mg once every week in patients weighing greater than or equal to 30 kg or subcutaneous 162 mg once every 2 weeks in patients weighing less than 30 kg.

Patients must have a minimum body weight of 10 kg when receiving tocilizumab subcutaneously.

pJIA patients

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

sJIA and pJIA patients

Dose adjustments due to laboratory abnormalities

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

- Liver enzyme abnormalities

Laboratory Value	Action
> 1 to 3 × ULN	Modify the dose of the concomitant MTX if appropriate. For persistent increases in this range, interrupt tocilizumab until ALT/AST have normalised.
> 3 × ULN to 5 × ULN	Modify the dose of the concomitant MTX if appropriate. Interrupt tocilizumab dosing until < 3 × ULN and follow recommendations above for > 1 to 3 × ULN.
> 5 × ULN	Discontinue tocilizumab. The decision to discontinue treatment in sJIA or pJIA for a laboratory abnormality must be based on the medical assessment of the individual patient.

- Low absolute neutrophil count (ANC)

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

- Low platelet count

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

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

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

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

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

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

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

The pre-filled syringe should not be shaken.

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

4.3 Contraindications

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

Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

RoActemra subcutaneous formulation is not intended for intravenous administration.

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

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

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

Vigilance for the timely detection of serious infection is recommended for patients receiving immunosuppressive agents such as tocilizumab as signs and symptoms of acute inflammation may be

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

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

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

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

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

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

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

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

Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, have been observed with tocilizumab (see section 4.8). Serious hepatic injury occurred between 2 weeks to more than 5 years after initiation of treatment. Cases of liver failure resulting in liver transplantation have been reported. Patients must be advised to immediately seek medical help if they experience signs and symptoms of hepatic injury.

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

In RA, GCA, pJIA and sJIA patients, ALT/AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended modifications, including tocilizumab discontinuation, based on transaminases levels see section 4.2. For ALT or AST elevations > 3–5 × ULN, treatment should be interrupted.

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

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

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

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

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

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

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

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

Malignancy
The risk of malignancy is increased in patients with RA. Immunomodulatory medicinal products may increase the risk of malignancy. The clinical data are insufficient to assess the potential incidence of malignancy following exposure to tocilizumab. Long-term safety evaluations are ongoing.

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

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

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

Polysorbate
This medicine contains 0.18 mg of polysorbate 80 in each 162 mg/0.9 mL syringe which is equivalent to 0.2 mg/mL. Polysorbates may cause allergic reactions. Patients' known allergies shall be taken into consideration.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

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

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

RoActemra should not be used during pregnancy unless clearly necessary.

Breast-feeding
It is unknown whether tocilizumab is excreted in human milk. The excretion of tocilizumab in milk has not been studied in animals. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from RoActemra therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The safety profile comes from 4510 patients exposed to tocilizumab in clinical trials; the majority of these patients were participating in adult RA trials (n=4009), while the remaining experience comes from GCA (n=149), pJIA (n=240) and sJIA (n=112) trials. The safety profile of tocilizumab across these indications remains similar and undifferentiated.

The most commonly reported adverse reactions were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

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

Tabulated list of adverse reactions
Adverse reactions from clinical trials and/or post-marketing experience with tocilizumab based on spontaneous case reports, literature cases and cases from non-interventional study programs are listed in Table 1 and are presented by MedDRA system organ class. The corresponding frequency category for each AR is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100) rare, (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), and frequency not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. List of adverse reactions occurring in patients treated with tocilizumab

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

MedDRA SOC	Frequency categories with preferred terms				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Investigations		Hepatic transaminases increased, Weight increased, Total bilirubin increased*			

* Includes elevations collected as part of routine laboratory monitoring (see text below)

[1] See section 4.3

[2] See section 4.4

[3] This adverse reaction was identified through post-marketing surveillance but not observed in controlled clinical trials. The frequency category was estimated as the upper limit of the 95% confidence interval calculated on the basis of the total number of patients exposed to tocilizumab in clinical trials.

Description of selected adverse reactions (subcutaneous use)

RA patients

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

Injection site reactions

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

Immunogenicity

In SC-I, a total of 625 patients treated with tocilizumab 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 neutralising anti-tocilizumab antibodies. One patient was tested positive for IgE isotype (0.2%).

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

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

Neutrophils

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

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

Platelets

During routine laboratory monitoring in the tocilizumab 6 month clinical trial SC-I, none of the patients on the subcutaneous weekly dose had a decrease in platelet count to $\leq 50 \times 10^3/\mu L$.

Hepatic transaminase elevations

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

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

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

Infections
The rate of infection in sJIA patients treated with subcutaneous tocilizumab was comparable to sJIA patients treated with intravenous tocilizumab.

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

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

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

Lipid parameters
In the 52-week open-label subcutaneous study (WA28118), 23.4% and 35.4% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL at any time during study treatment, respectively.

pJIA patients
The safety profile of subcutaneous tocilizumab was also evaluated in 52 paediatric patients with pJIA. The total patient exposure to tocilizumab in the pJIA all exposure population was 184.4 patient years for intravenous and 50.4 patient years for subcutaneous tocilizumab. In general, the safety profile observed in patients with pJIA was consistent with the known safety profile of tocilizumab with the exception of ISRs (see Table 1). A higher frequency of pJIA patients experienced ISRs following subcutaneous injections compared to adult RA.

Infections
In the subcutaneous tocilizumab study, the rate of infection in pJIA patients treated with subcutaneous treatment was comparable with pJIA patients treated with intravenous treatment.

Injection Site Reactions
A total of 28.8% (15/52) pJIA patients experienced ISRs to tocilizumab subcutaneous. These ISRs occurred in a 44% of patients ≥ 30 kg compared to 14.8% of patients below 30 kg. The most common

ISRs were injection site erythema, swelling, haematoma, pain and pruritis. All ISRs reported were non-serious Grade 1 events, and none of the ISRs required patient withdrawal from treatment or dose interruption.

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

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

Lipid parameters
In the subcutaneous study, 14.3% and 12.8% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL at any time during study treatment, respectively.

GCA patients
The safety of subcutaneous tocilizumab has been studied in one Phase III study (WA28119) with 251 GCA patients. The total patient years duration in the tocilizumab 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 treatment groups was consistent with the known safety profile of tocilizumab (see Table 1).

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

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

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

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

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

Hepatic transaminase elevations

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

Lipid parameters

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

Description of selected adverse reactions (intravenous use)

RA patients

The safety of tocilizumab 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 two years is reached. The control period in 4 of the trials was 6 months and in 1 study was up to 2 years. In the double-blind controlled trials 774 patients received tocilizumab 4 mg/kg in combination with MTX, 1870 patients received tocilizumab 8 mg/kg in combination with MTX/other DMARDs and 288 patients received tocilizumab 8 mg/kg monotherapy.

The *all exposure* population includes all patients who received at least one dose of tocilizumab either in the double-blind control period or open label extension phase in trials. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3296 for at least one year; 2806 received treatment for at least 2 years and 1222 for 3 years.

Infections

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

In 6-month controlled clinical trials, the rate of serious infections with tocilizumab 8 mg/kg plus DMARDs was 5.3 events per 100 patient years exposure compared to 3.9 events per 100 patient years exposure in the placebo plus DMARD group. In the monotherapy study the rate of serious infections was 3.6 events per 100 patient years of exposure in the tocilizumab group and 1.5 events per 100 patient years of exposure in the MTX group.

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

Interstitial lung disease

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

Gastrointestinal perforation

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

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

The rate of anaphylactic reactions (occurring in a total of 6/3778 patients, 0.2%) was several fold higher with the 4 mg/kg dose, compared to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported in a total of 13 out of 3778 patients (0.3%) treated during the controlled and open label clinical trials. These reactions were generally observed during the second to fifth infusions of tocilizumab (see section 4.4). Fatal anaphylaxis has been reported after marketing authorisation during treatment with intravenous tocilizumab (see section 4.4).

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

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

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

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

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

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

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

The addition of potentially hepatotoxic medicinal products (e.g. MTX) to tocilizumab monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST > 5 × ULN were observed

in 0.7% of tocilizumab monotherapy patients and 1.4% of tocilizumab plus DMARD patients, the majority of whom were discontinued permanently from tocilizumab treatment. During the double-blind controlled period, the incidence of indirect bilirubin greater than the upper limit of normal, collected as a routine laboratory parameter, is 6.2% in patients treated with 8 mg/kg tocilizumab + DMARD. A total of 5.8% of patients experienced an elevation of indirect bilirubin of > 1 to 2 × ULN and 0.4% had an elevation of > 2 × ULN.

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

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

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Pharmacodynamic effects
In clinical trials with tocilizumab, rapid decreases in CRP, erythrocyte sedimentation rate (ESR), serum amyloid A (SAA) and fibrinogen were observed. Consistent with the effect on acute phase reactants, treatment with tocilizumab was associated with reduction in platelet count within the normal range. Increases in haemoglobin levels were observed, through tocilizumab decreasing the IL-6 driven effects on hepcidin production to increase iron availability. In treated patients, decreases in the levels of CRP to within normal ranges were seen as early as week 2, with decreases maintained while on treatment.

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

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

RA (Subcutaneous use)
Clinical efficacy

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

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

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

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

	SC-I[a]	
	TCZ SC 162 mg every week + DMARD N=558	TCZ IV 8 mg/kg + DMARD N=537
ACR 20 week 24	69.4%	73.4%
Weighted difference (95% CI)	-4.0 (-9.2, 1.2)	
ACR 50 week 24	47.0%	48.6%
Weighted difference (95% CI)	-1.8 (-7.5, 4.0)	
ACR 70 week 24	24.0%	27.9%
Weighted difference (95% CI)	-3.8 (-9.0, 1.3)	

DMARD = disease-modifying anti-rheumatic drugs
TCZ = tocilizumab
IV = intravenous
SC = subcutaneous
a = Per Protocol Population

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

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

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

In study SC-II, at week 24 there was ACR 20 of 60.9%, ACR 50 of 39.8% and ACR 70 of 19.7% for patients treated with tocilizumab subcutaneous every other week versus placebo ACR 20 of 31.5%, ACR 50 of 12.3% and ACR 70 of 5.0%. Patients had mean DAS28 at baseline of 6.7 on subcutaneous and 6.6 on placebo arms. At week 24, a significant reduction in DAS28 from baseline of 3.1 was observed on subcutaneous and 1.7 on placebo arm, and for DAS28 < 2.6, 32.0% was observed on subcutaneous and 4.0% on placebo arm.

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

In study SC-II, mean decrease in HAQ-DI from baseline to week 24 was significantly greater for patients treated with tocilizumab subcutaneous every other week (0.4) versus placebo (0.3). Proportion of patients achieving a clinically relevant improvement in HAQ-DI at week 24 (change from baseline of ≥ 0.3 units) was higher for subcutaneous treatment every other week (58%) versus placebo (46.8%). SF-36 (mean change in mental and physical component scores) was significantly greater with tocilizumab subcutaneous group (6.5 and 5.3) versus placebo (3.8 and 2.9).

sJIA (subcutaneous)
Clinical efficacy

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

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

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

pJIA (subcutaneous)
Clinical efficacy

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

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

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

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

GCA (subcutaneous)
Clinical efficacy

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

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

Two subcutaneous doses of tocilizumab (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 tocilizumab -treated groups and one of the placebo-treated groups followed a pre-specified prednisone-taper regimen over

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

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

Table 3. Duration of corticosteroid therapy during screening in Study WA28119

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

SC = subcutaneous

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

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

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

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

Secondary endpoints

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

Cumulative glucocorticoid dose

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

Table 4. Efficacy results from Study WA28119

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

* $p < 0.0001$

** $p < 0.005$ (threshold for significance for primary and key secondary tests of superiority)

***Descriptive p value < 0.005

****Flare: recurrence of GCA signs or symptoms and/or ESR ≥ 30 mm/h – Increase in the prednisone dose required

Remission: absence of flare and normalization of the CRP

Sustained remission: remission from week 12 to week 52 –Patients must adhere to the protocol-defined prednisone taper

[1] analysis of the time (in days) between clinical remission and first disease flare

[2] p-values are determined using a Van Elteren analysis for non-parametric data

[§] statistical analyses has not been performed

N/A=Not applicable

HR=Hazard Ratio

CI=Confidence Interval

SC=subcutaneous

Quality of life outcomes

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

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

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

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

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

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

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

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

Study II, a two year study with planned analyses at week 24, week 52 and week 104, evaluated 1196 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of tocilizumab or placebo were given every four weeks as blinded therapy for 52 weeks in combination with stable MTX (10 mg to 25 mg weekly). After week 52, all patients could receive open-label treatment with tocilizumab 8 mg/kg. Of the patients who completed the study who were originally randomised to placebo + MTX, 86% received open-label tocilizumab 8 mg/kg in year 2. The primary endpoint at week 24 was the proportion of patients who achieved an ACR 20 response. At week 52 and week 104 the co-primary endpoints were prevention of joint damage and improvement in physical function.

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

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

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

Clinical response

In all trials, patients treated with tocilizumab 8 mg/kg had statistically significant higher ACR 20, 50, 70 response rates at 6 months compared to control (Table 5). In study I, superiority of tocilizumab 8 mg/kg was demonstrated against the active comparator MTX.

The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race, number of prior treatments or disease status. Time to onset was rapid (as early as week 2) and the magnitude of response continued to improve with duration of treatment. Continued durable responses were seen for over 3 years in the open label extension trials I-V.

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

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

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

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

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

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

Major clinical response
After 2 years of treatment with tocilizumab plus MTX, 14% of patients achieved a major clinical response (maintenance of an ACR 70 response for 24 weeks or more).

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

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

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

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

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

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

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

Haemoglobin levels
Statistically significant improvements in haemoglobin levels were observed with tocilizumab compared with DMARDs ($p < 0.0001$) at week 24. Mean haemoglobin levels increased by week 2 and remained within normal range through to week 24.

Tocilizumab versus adalimumab in monotherapy
Study VI (WA19924), a 24-week double-blinded study that compared tocilizumab monotherapy with adalimumab monotherapy, evaluated 326 patients with RA who were intolerant of MTX or where continued treatment with MTX was considered inappropriate (including MTX inadequate responders). Patients in the tocilizumab arm received an intravenous infusion of tocilizumab (8 mg/kg) every 4 weeks (q4w) and a subcutaneous placebo injection every 2 weeks (q2w). Patients in the adalimumab arm received an adalimumab subcutaneous injection (40 mg) q2w plus an intravenous placebo infusion q4w.

A statistically significant superior treatment effect was seen in favour of tocilizumab over adalimumab in control of disease activity from baseline to week 24 for the primary endpoint of change in DAS28 and for all secondary endpoints (Table 7).

Table 7. Efficacy Results for Study VI (WA19924)

	ADA + Placebo (IV) N = 162	TCZ + Placebo (SC) N = 163	p-value[(a)]
Primary Endpoint – Mean Change from baseline at week 24			
DAS28 (adjusted mean)	-1.8	-3.3	
Difference in adjusted mean (95% CI)	-1.5 (-1.8, -1.1)		<0.0001
Secondary Endpoints – Percentage of Responders at week 24 [(b)]			
DAS28 < 2.6, n (%)	17 (10.5)	65 (39.9)	<0.0001
DAS28 ≤ 3.2, n (%)	32 (19.8)	84 (51.5)	<0.0001
ACR 20 response, n (%)	80 (49.4)	106 (65.0)	0.0038
ACR 50 response, n (%)	45 (27.8)	77 (47.2)	0.0002
ACR 70 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
IV = intravenous
SC = subcutaneous
ADA = adalimumab
TCZ = tocilizumab

The overall clinical adverse event profile was similar between tocilizumab and adalimumab. The proportion of patients with serious adverse events was balanced between the treatment groups (tocilizumab 11.7% vs. adalimumab 9.9%). The types of adverse reactions in the tocilizumab arm were consistent with the known safety profile of tocilizumab and adverse reactions were reported at a similar frequency compared with Table 1. A higher incidence of infections and infestations was reported in the tocilizumab arm (48% vs. 42%), with no difference in the incidence of serious infections (3.1%). Both study treatments induced the same pattern of changes in laboratory safety parameters (decreases in neutrophil and platelet counts, increases in ALT, AST and lipids), however, the magnitude of change and the frequency of marked abnormalities was higher with tocilizumab compared with adalimumab. Four (2.5%) patients in the tocilizumab arm and two (1.2%) patients in the adalimumab arm experienced CTC grade 3 or 4 neutrophil count decreases. Eleven (6.8%) patients in the tocilizumab arm and five (3.1%) patients in the adalimumab arm experienced ALT increases of CTC grade 2 or higher. The mean LDL increase from baseline was 0.64 mmol/L (25 mg/dL) for patients in the tocilizumab arm and 0.19 mmol/L (7 mg/dL) for patients in the adalimumab arm. The safety observed in the tocilizumab arm was consistent with the known safety profile of tocilizumab and no new or unexpected adverse reactions were observed (see Table 1).

5.2 Pharmacokinetic properties

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

RA
Intravenous use
The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 3552 RA patients treated with a one-hour infusion of 4 or 8 mg/kg

tocilizumab every 4 weeks for 24 weeks or with 162 mg tocilizumab given subcutaneously either once a week or every other week for 24 weeks.

The following parameters (predicted mean ± SD) were estimated for a dose of 8 mg/kg tocilizumab given every 4 weeks: steady-state area under curve (AUC) = 38000 ± 13000 h•µg/mL, trough concentration (C_{min}) = 15.9 ± 13.1 µg/mL and maximum concentration (C_{max}) = 182 ± 50.4 µg/mL, and. The accumulation ratios for AUC and C_{max} were small, 1.32 and 1.09, respectively. The accumulation ratio was higher for C_{min} (2.49), which was expected based on the non-linear clearance contribution at lower concentrations. Steady-state was reached following the first administration for C_{max} and after 8 and 20 weeks for AUC and C_{min}, respectively. Tocilizumab AUC, C_{min} and C_{max} increased with increase of body weight. At body weight ≥ 100 kg, the predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 50000 ± 16800 µg•h/mL, 24.4 ± 17.5 µg/mL, and 226 ± 50.3 µg/mL, respectively, which are higher than mean exposure values for the patient population (i.e. all body weights) reported above. The dose-response curve for tocilizumab flattens at higher exposure, resulting in smaller efficacy gains for each incremental increase in concentration such that clinically meaningful increases in efficacy were not demonstrated in patients treated with > 800 mg of tocilizumab. Therefore, doses exceeding 800 mg per infusion are not recommended (see section 4.2).

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

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

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

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

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

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

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

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

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

sJIA patients
Subcutaneous use
The pharmacokinetics of tocilizumab in sJIA patients was characterised by a population pharmacokinetic analysis which included 140 patients who were treated with 8 mg/kg intravenous every 2 weeks (patients weighing ≥ 30 kg), 12 mg/kg intravenous every 2 weeks (patients weighing below 30 kg), 162 mg subcutaneous every week (patients weighing ≥ 30 kg), 162 mg subcutaneous every 10 days or every 2 weeks (patients weighing below 30 kg).

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

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

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

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

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

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

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

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

pJIA patients

Subcutaneous use

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

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

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

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

After intravenous dosing, approximately 90% of the steady-state was reached by week 12 for the 10 mg/kg (body weight < 30 kg), and by week 16 for the 8 mg/kg (body weight ≥ 30 kg) dose. After subcutaneous dosing, approximately 90% of the steady-state was reached by week 12 for both the 162 mg subcutaneous Q2W and Q3W regimens.

Absorption

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

Distribution

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

Elimination

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

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

GCA patients

Subcutaneous use

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

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

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

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

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

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

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

Absorption
Following subcutaneous dosing in GCA patients, the absorption t½ was around 4 days. The bioavailability for the subcutaneous formulation was 0.8. 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
In GCA patients, the central volume of distribution was 4.09 L, the peripheral volume of distribution was 3.37 L, resulting in a volume of distribution at steady-state of 7.46 L.

Elimination
The total clearance of 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 6.7 mL/h in GCA patients,

In GCA patients, at steady-state, the effective t ½ 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 weekly regimen. At high serum concentrations, when total clearance of tocilizumab is dominated by linear clearance, an effective $t_{½}$ of approximately 32 days was derived from the population parameter estimates.

Special populations
Renal impairment
No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab has been conducted. Most of the patients in the RA and GCA population pharmacokinetic analyses 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 tocilizumab.

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

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

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

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

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

5.3 Preclinical safety data

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

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine (for pH-adjustment)
L-Histidine monohydrochloride monohydrate (for pH-adjustment)
L-Arginine/L-Arginine hydrochloride
L-Methionine
Polysorbate 80 (E 433)
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

3 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C). Do not freeze. Once removed from the refrigerator, the pre-filled syringe can be stored up to 2 weeks at or below 30 °C.

Keep the pre-filled syringe in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

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

Pack sizes of 4 pre-filled syringes and multipacks containing 12 (3 packs of 4) pre-filled syringes.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

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

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

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/007
EU/1/08/492/008

9. DATE OF FIRST AUTHORISATION/DATE OF LATEST RENEWAL

Date of first authorisation: 16 January 2009
Date of last renewal: 25 September 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 162 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 162 mg of RoActemra (tocilizumab) in 0.9 mL.

RoActemra is a recombinant humanised, anti-human monoclonal antibody of the immunoglobulin G1 (IgG1) sub-class.

Excipient with known effects
Each 162 mg/0.9 mL pre-filled pen contains 0.18 mg (0.2 mg/mL) polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in pre-filled pen (ACTPen).

A colourless to slightly yellowish solution with a pH of 5.5-6.5 and an osmolality of 200-372 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis (RA)
RoActemra, in combination with methotrexate (MTX), is indicated for

- the treatment of severe, active and progressive RA in adults not previously treated with MTX.
- the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

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

Systemic juvenile idiopathic arthritis (sJIA)
RoActemra is indicated for the treatment of active sJIA in patients 12 years of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids (see Section 4.2).
RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Polyarticular juvenile idiopathic arthritis (pJIA)
RoActemra in combination with MTX is indicated for the treatment of pJIA (rheumatoid factor positive or negative and extended oligoarthritis) in patients 12 years of age and older, who have responded inadequately to previous therapy with MTX (see Section 4.2).

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

Giant cell arteritis (GCA)
RoActemra is indicated for the treatment of GCA in adult patients.

4.2 Posology and method of administration

Tocilizumab subcutaneous formulation is administered with a single-use pre-filled pen. Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA, sJIA, pJIA and/or GCA.

The pre-filled pen should not be used to treat paediatric patients < 12 years of age since there is a potential risk of intramuscular injection due to thinner subcutaneous tissue layer.
The first injection should be performed under the supervision of a qualified health care professional. A patient or parent/guardian can inject this medicinal product only if the physician determines that it is appropriate and the patient or parent/guardian agrees to medical follow-up as necessary and has been trained in proper injection technique.

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

All patients treated with RoActemra must be given the Patient Card.

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

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

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

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

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

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

RA and GCA patients
Dose adjustments due to laboratory abnormalities (see section 4.4).

- Liver enzyme abnormalities

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

- Low absolute neutrophil count (ANC)

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

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

- Low platelet count

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

RA and GCA patients
Missed dose

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

Special populations
Elderly
No dose adjustment is required in elderly patients > 65 years of age.

Renal impairment
No dose adjustment is required in patients with mild or moderate renal impairment. Tocilizumab has not been studied in patients with severe renal impairment (see section 5.2). Renal function must be monitored closely in these patients.

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

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

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

sJIA patients
The recommended posology in patients above 12 years of age is 162 mg subcutaneously once every week in patients weighing greater than or equal to 30 kg or 162 mg subcutaneously once every 2 weeks in patients weighing less than 30 kg.

The pre-filled pen should not be used to treat paediatric patients < 12 years of age.

Patients must have a minimum body weight of 10 kg when receiving tocilizumab subcutaneously.

pJIA patients
The recommended posology in patients above 12 years of age is 162 mg subcutaneously once every 2 weeks in patients weighing greater than or equal to 30 kg or 162 mg subcutaneously once every 3 weeks in patients weighing less than 30 kg.

The pre-filled pen should not be used to treat paediatric patients < 12 years of age.

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

- Liver enzyme abnormalities

Laboratory Value	Action
> 1 to 3 × ULN	Modify the dose of the concomitant MTX if appropriate. For persistent increases in this range, interrupt tocilizumab until ALT/AST have normalised.
> 3 × ULN to 5 × ULN	Modify the dose of the concomitant MTX if appropriate. Interrupt tocilizumab dosing until < 3 × ULN and follow recommendations above for > 1 to 3 × ULN.
> 5 × ULN	Discontinue tocilizumab. The decision to discontinue treatment in sJIA or pJIA for a laboratory abnormality must be based on the medical assessment of the individual patient.

- Low absolute neutrophil count (ANC)

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

- Low platelet count

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

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

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

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

Missed dose

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

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

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

The pre-filled pen should not be shaken.

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

4.3 Contraindications

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

Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

RoActemra subcutaneous formulation is not intended for intravenous administration.

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

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

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

Vigilance for the timely detection of serious infection is recommended for patients receiving immunosuppressive agents such as tocilizumab as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute phase reactants. The effects of tocilizumab on C-reactive protein (CRP), neutrophils and signs and symptoms of infection must be considered when evaluating a patient for a potential infection. Patients, (which includes younger children with sJIA or pJIA who may be less able to communicate their symptoms) and parents/guardians of sJIA or pJIA patients,

should be instructed to contact their healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

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

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

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

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

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

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

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

Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, have been observed with tocilizumab (see section 4.8). Serious hepatic injury occurred between 2 weeks to more than 5 years after initiation of treatment. Cases of liver failure resulting in liver transplantation have been reported. Patients must be advised to immediately seek medical help if they experience signs and symptoms of hepatic injury.

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

In RA, GCA, pJIA and sJIA patients, ALT/AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended modifications, including tocilizumab discontinuation, based on transaminases levels see section 4.2. For ALT or AST elevations > 3-5 × ULN, treatment should be interrupted.

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

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

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

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

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

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

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

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

Malignancy
The risk of malignancy is increased in patients with RA. Immunomodulatory medicinal products may increase the risk of malignancy. The clinical data are insufficient to assess the potential incidence of malignancy following exposure to tocilizumab. Long-term safety evaluations are ongoing.

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

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

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

Polysorbates
This medicine contains 0.18 mg of polysorbate 80 in each 162 mg/0.9 mL PFP which is equivalent to 0.2 mg/mL. Polysorbates may cause allergic reactions. Patients' known allergies shall be taken into consideration.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

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

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

RoActemra should not be used during pregnancy unless clearly necessary.

Breast-feeding
It is unknown whether tocilizumab is excreted in human milk. The excretion of tocilizumab in milk has not been studied in animals. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from RoActemra therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The safety profile comes from 4510 patients exposed to tocilizumab in clinical trials; the majority of these patients were participating in RA studies (n=4009), while the remaining experience comes from GCA (n=149), pJIA (n=240) and sJIA (n=112) studies. The safety profile of tocilizumab across these indications remains similar and undifferentiated.

The most commonly reported Adverse reactions were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

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

Tabulated list of adverse reactions
Adverse reactions from clinical trials and/or post-marketing experience with tocilizumab based on spontaneous case reports, literature cases and cases from non-interventional study programs are listed in Table 1 and are presented by MedDRA system organ class. The corresponding frequency category 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), and frequency not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. List of adverse reactions occurring in patients treated with tocilizumab

MedDRA SOC	Frequency category with preferred term				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Infections and infestations	Upper respiratory tract infections	Cellulitis, Pneumonia, Oral herpes simplex, Herpes zoster	Diverticulitis		
Blood and lymphatic system disorders		Leukopenia, Neutropenia, Hypofibrinogenaemia			
Immune system disorders				Anaphylaxis (fatal)[1, 2 ,3]	
Endocrine disorders			Hypothyroidism		
Metabolism and nutrition disorders	Hypercholesterolaemia*		Hypertriglyceridaemia		
Nervous system disorders		Headache, Dizziness			
Eye disorders		Conjunctivitis			
Vascular disorders		Hypertension			
Respiratory, thoracic and mediastinal disorders		Cough, Dyspnoea			
Gastrointestinal disorders		Abdominal pain, Mouth ulceration, Gastritis	Stomatitis, Gastric ulcer		

MedDRA SOC	Frequency category with preferred term				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Hepatobiliary disorders				Drug-induced liver injury, Hepatitis, Jaundice	Hepatic failure
Skin and subcutaneous tissue disorders		Rash, Pruritus, Urticaria		Stevens-Johnson-Syndrome[3]	
Renal and urinary disorders			Nephrolithiasis		
General disorders and administration site conditions	Injection site reaction	Peripheral oedema Hypersensitivity reaction,			
Investigations		Hepatic transaminases increased, Weight increased, Total bilirubin increased*			

* Includes elevations collected as part of routine laboratory monitoring (see text below)
[1] See section 4.3
[2] See section 4.4
[3] This adverse reaction was identified through post-marketing surveillance but not observed in controlled clinical trials. The frequency category was estimated as the upper limit of the 95% confidence interval calculated on the basis of the total number of patients exposed to TCZ in clinical trials.

Description of selected adverse reactions (subcutaneous use)

RA patients

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

Injection site reactions

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

Immunogenicity

In SC-I, a total of 625 patients treated with tocilizumab 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 neutralising anti- tocilizumab antibodies. One patient was tested positive for IgE isotype (0.2%).

In SC-II, a total of 434 patients treated with tocilizumab 162 mg every other week were tested for anti-tocilizumab antibodies in the 6 month controlled period. Seven patients (1.6%) developed positive

anti-tocilizumab antibodies; of these, six (1.4%) developed neutralising anti-tocilizumab antibodies. Four patients were tested positive for IgE isotype (0.9%).

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

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

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

Platelets
During routine laboratory monitoring in the tocilizumab 6 month clinical trial SC-I, none of the patients on the subcutaneous weekly dose had a decrease in platelet count to $\leq 50 \times 10^3$/μL.

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

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

sJIA patients The safety profile of subcutaneous tocilizumab was evaluated in 51 paediatric patients (1 to 17 years of age) with sJIA. In general, the adverse reactions in patients with sJIA were similar in type to those seen in RA patients (see section 4.8).

Infections
The rate of infection in sJIA patients treated with subcutaneous tocilizumab was comparable to sJIA patients treated with intravenous tocilizumab.

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

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

Laboratory abnormalities
In the 52-week open-label subcutaneous study (WA28118), neutrophil count decrease to below 1×10^9/L occurred in 23.5% of patients treated with tocilizumab subcutaneous. Decreases in platelet counts to below 100×10^3/μL occurred in 2% of the patients treated with tocilizumab subcutaneous. An elevation in ALT or AST to $\geq 3 \times$ ULN occurred in 9.8% and 4.0% patients treated with tocilizumab subcutaneous, respectively.

Lipid parameters

In the 52-week open-label subcutaneous study (WA28118), 23.4% and 35.4% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL at any time during study treatment, respectively.

pJIA patients
The safety profile of subcutaneous tocilizumab was also evaluated in 52 paediatric patients with pJIA. The total patient exposure to tocilizumab in the pJIA all exposure population was 184.4 patient years for intravenous and 50.4 patient years for subcutaneous tocilizumab. In general, the safety profile observed in patients with pJIA was consistent with the known safety profile of tocilizumab with the exception of ISRs (see Table 1). A higher frequency of pJIA patients experienced ISRs following subcutaneous injections compared to adult RA.

Infections
In the subcutaneous tocilizumab study, the rate of infection in pJIA patients treated with subcutaneous tocilizumab was comparable with pJIA patients treated with intravenous tocilizumab.

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

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

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

Lipid parameters
In the subcutaneous study, 14.3% and 12.8% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL at any time during study treatment, respectively.

GCA patients
The safety of subcutaneous tocilizumab has been studied in one Phase III study (WA28119) with 251 GCA patients. The total patient years duration in the treatment 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 treatment groups was consistent with the known safety profile of tocilizumab (see Table 1).

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

Injection site reactions

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

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

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

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

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

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

Description of selected adverse reactions (intravenous use)
RA patients
The safety of tocilizumab has been studied in 4 placebo-controlled studies (studies II, III, IV and V), 1 MTX-controlled study (study I) and their extension periods (see section 5.1).

The double-blind controlled period was 6 months in four studies (studies I, III, IV and V) and was up to 2 years in one study (study II). In the double-blind controlled studies, 774 patients received tocilizumab 4 mg/kg in combination with MTX, 1870 patients received tocilizumab 8 mg/kg in combination with MTX or other DMARDs and 288 patients received tocilizumab 8 mg/kg monotherapy.

The long-term exposure population includes all patients who received at least one dose of tocilizumab either in the double-blind control period or open label extension phase in the studies. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3296 for at least one year, 2806 received treatment for at least 2 years and 1222 for 3 years.

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

In 6-month controlled clinical trials, the rate of serious infections with tocilizumab 8 mg/kg plus DMARDs was 5.3 events per 100 patient years exposure compared to 3.9 events per 100 patient years exposure in the placebo plus DMARD group. In the monotherapy study the rate of serious infections was 3.6 events per 100 patient years of exposure in the tocilizumab group and 1.5 events per 100 patient years of exposure in the MTX group.

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

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

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

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

The rate of anaphylactic reactions (occurring in a total of 8/4,009 patients, 0.2%) was several fold higher with the 4 mg/kg dose, compared to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported in a total of 56 out of 4,009 patients (1.4%) treated during the controlled and open label clinical trials. These reactions were generally observed during the second to fifth infusions of tocilizumab (see section 4.4). Fatal anaphylaxis has been reported after marketing authorisation during treatment with intravenous tocilizumab (see section 4.4).

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

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

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

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

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

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

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

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

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

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

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Pharmacodynamic effects
In RA clinical trials with tocilizumab, rapid decreases in CRP, erythrocyte sedimentation rate (ESR), serum amyloid A (SAA) and fibrinogen were observed. Consistent with the effect on acute phase reactants, treatment with tocilizumab was associated with reduction in platelet count within the normal range. Increases in haemoglobin levels were observed, through tocilizumab decreasing the IL-6 driven effects on hepcidin production to increase iron availability. In treated patients, decreases in the levels of CRP to within normal ranges were seen as early as week 2, with decreases maintained while on treatment.

In GCA clinical study WA28119, similar rapid decreases in CRP and ESR were observed along with slight increases in mean corpuscular haemoglobin concentration. In healthy subjects administered tocilizumab in doses from 2 to 28 mg/kg intravenously and 81 to 162 mg subcutaneously, absolute neutrophil counts decreased to their lowest 2 to 5 days following administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. RA and GCA patients demonstrate a comparable (to healthy subjects) decrease of absolute neutrophil counts following tocilizumab administration (see section 4.8).

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

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

Clinical response
Study SC-I evaluated patients with moderate to severe active RA who had an inadequate clinical response to their existing rheumatologic therapy, including one or more DMARD(s) where approximately 20% had a history of inadequate response to at least one TNF inhibitor. In SC-I, 1262 patients were randomised 1:1 to receive tocilizumab subcutaneous 162 mg every week or

tocilizumab intravenous 8 mg/kg every four weeks in combination with non-biologic DMARD(s). The primary endpoint in the study was the difference in the proportion of patients who achieved an ACR 20 response at week 24. The results from study SC-I is shown in Table 2.

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

	SC-I[a]	
	TCZ SC 162 mg every week + DMARD N=558	TCZ IV 8 mg/kg + DMARD N=537
ACR 20 week 24	69.4%	73.4%
Weighted difference (95% CI)	-4.0 (-9.2, 1.2)	
ACR 50 week 24	47.0%	48.6%
Weighted difference (95% CI)	-1.8 (-7.5, 4.0)	
ACR 70 week 24	24.0%	27.9%
Weighted difference (95% CI)	-3.8 (-9.0, 1.3)	

TCZ = tocilizumab
IV = intravenous
SC = subcutaneous
a = Per Protocol Population

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

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

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

In study SC-II, at week 24 there was ACR 20 of 60.9%, ACR 50 of 39.8% and ACR 70 of 19.7% for patients treated with tocilizumab subcutaneous every other week versus placebo ACR 20 of 31.5%, ACR 50 of 12.3% and ACR 70 of 5.0%. Patients had mean DAS28 at baseline of 6.7 on subcutaneous and 6.6 on placebo arms. At week 24, a significant reduction in DAS28 from baseline of 3.1 was observed on subcutaneous and 1.7 on placebo arm, and for DAS28 < 2.6, 32.0% was observed on subcutaneous and 4.0% on placebo arm.

Health-related and quality of life outcomes
In study SC-I, the mean decrease in HAQ-DI from baseline to week 24 was 0.6 on both the subcutaneous and intravenous arms. The proportion of patients achieving a clinically relevant improvement in HAQ-DI at week 24 (change from baseline of ≥ 0.3 units) was also comparable on the

subcutaneous (65.2%) versus intravenous (67.4%) arms, with a weighted difference in proportions of - 2.3% (95% CI - 8.1, 3.4). For SF-36, the mean change from baseline at week 24 in the mental component score was 6.22 for the subcutaneous arm and 6.54 for the intravenous arm, and for the physical component score was also similar with 9.49 for the subcutaneous arm and 9.65 for the intravenous arm.

In study SC-II, mean decrease in HAQ-DI from baseline to week 24 was significantly greater for patients treated with tocilizumab subcutaneous every other week (0.4) versus placebo (0.3). Proportion of patients achieving a clinically relevant improvement in HAQ-DI at week 24 (change from baseline of ≥ 0.3 units) was higher for tocilizumab subcutaneous every other week (58%) versus placebo (46.8%). SF-36 (mean change in mental and physical component scores) was significantly greater with tocilizumab subcutaneous group (6.5 and 5.3) versus placebo (3.8 and 2.9).

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

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

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

Subcutaneous use
pJIA patients
Clinical efficacy
A 52-week, open-label, multi-centre, PK-PD and safety study was conducted in paediatric patients with pJIA, aged 1 to 17 years old, to determine the appropriate subcutaneous dose of tocilizumab that achieved comparable PK/PD and safety profiles to the intravenous regimen.

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

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

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

Subcutaneous use

GCA patients

Clinical efficacy

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

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

Two subcutaneous doses of tocilizumab (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 tocilizumab-treated groups and one of the placebo-treated groups followed a pre-specified prednisone-taper regimen over 26 weeks, while the second placebo-treated group followed a pre-specified prednisone-taper regimen over 52 weeks, designed to be more in keeping with standard practice.

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

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

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

SC = subcutaneous

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

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

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

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

Secondary endpoints

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

Cumulative glucocorticoid dose

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

Table 4. Efficacy results from Study WA28119

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

* $p < 0.0001$

** $p < 0.005$ (threshold for significance for primary and key secondary tests of superiority)

***Descriptive p value ≤ 0.005

****Flare: recurrence of GCA signs or symptoms and/or ESR ≥ 30 mm/h – Increase in the prednisone dose required

Remission: absence of flare and normalization of the CRP

Sustained remission: remission from week 12 to week 52 –Patients must adhere to the protocol-defined prednisone taper

[1] analysis of the time (in days) between clinical remission and first disease flare

[2] p-values are determined using a Van Elteren analysis for non-parametric data

[§] statistical analyses has not been performed

N/A= Not applicable

HR = Hazard Ratio

CI = Confidence Interval

SC = subcutaneous

Quality of life outcomes

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

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

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

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

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

Intravenous use

RA patients

Clinical efficacy

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

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

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

Study II, a two year study with planned analyses at week 24, week 52 and week 104, evaluated 1196 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of tocilizumab or placebo were given every four weeks as blinded therapy for 52 weeks in combination with stable MTX (10 mg to 25 mg weekly). After week 52, all patients could receive open-label treatment with tocilizumab 8 mg/kg. Of the patients who completed the study who were originally randomised to placebo + MTX, 86% received open-label tocilizumab 8 mg/kg in year 2. The primary endpoint at

week 24 was the proportion of patients who achieved an ACR 20 response. At week 52 and week 104 the co-primary endpoints were prevention of joint damage and improvement in physical function.

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

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

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

Clinical response
In all studies, patients treated with tocilizumab 8 mg/kg had statistically significant higher ACR 20, 50, 70 response rates at 6 months compared to control (Table 5). In study I, superiority of tocilizumab 8 mg/kg was demonstrated against the active comparator MTX.

The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race, number of prior treatments or disease status. Time to onset was rapid (as early as week 2) and the magnitude of response continued to improve with duration of treatment. Continued durable responses were seen for over 3 years in the ongoing open label extension studies I-V.

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

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

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

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

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

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

Major clinical response
After 2 years of treatment with tocilizumab plus MTX, 14% of patients achieved a major clinical response (maintenance of an ACR 70 response for 24 weeks or more).

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

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

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

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

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

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

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

Haemoglobin levels
Statistically significant improvements in haemoglobin levels were observed with tocilizumab compared with DMARDs ($p < 0.0001$) at week 24. Mean haemoglobin levels increased by week 2 and remained within normal range through to week 24.

Tocilizumab versus adalimumab in monotherapy
Study VI (WA19924), a 24 week double-blinded study that compared tocilizumab monotherapy with adalimumab monotherapy, evaluated 326 patients with RA who were intolerant of MTX or where continued treatment with MTX was considered inappropriate (including MTX inadequate responders). Patients in the tocilizumab arm received an intravenous infusion of tocilizumab (8 mg/kg) every 4 weeks (q4w) and a subcutaneous placebo injection every 2 weeks (q2w). Patients in the adalimumab arm received an adalimumab subcutaneous injection (40 mg) q2w plus an intravenous placebo infusion q4w.
A statistically significant superior treatment effect was seen in favour of tocilizumab over adalimumab in control of disease activity from baseline to week 24 for the primary endpoint of change in DAS28 and for all secondary endpoints (Table 7).

Table 7: Efficacy results for Study VI (WA19924)

	ADA + Placebo (IV) N = 162	**TCZ + Placebo (SC) N = 163**	**p-value[(a)]**
Primary endpoint - Mean change from baseline at week 24			
DAS28 (adjusted mean)	-1.8	-3.3	
Difference in adjusted mean (95% CI)	-1.5 (-1.8, -1.1)		<0.0001
Secondary endpoints - Percentage of responders at week 24 [(b)]			
DAS28 < 2.6, n (%)	17 (10.5)	65 (39.9)	<0.0001
DAS28 ≤ 3.2, n (%)	32 (19.8)	84 (51.5)	<0.0001
ACR 20 response, n (%)	80 (49.4)	106 (65.0)	0.0038
ACR 50 response, n (%)	45 (27.8)	77 (47.2)	0.0002
ACR 70 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
IV = intravenous
SC = subcutaneous
ADA = adalimumab
TCZ = tocilizumab

The overall clinical adverse event profile was similar between tocilizumab and adalimumab. The proportion of patients with serious adverse events was balanced between the treatment groups (tocilizumab 11.7% vs. adalimumab 9.9%). The types of adverse reactions in the tocilizumab arm were consistent with the known safety profile of tocilizumab and adverse reactions were reported at a similar frequency compared with Table 1. A higher incidence of infections and infestations was reported in the tocilizumab arm (48% vs. 42%), with no difference in the incidence of serious infections (3.1%). Both study treatments induced the same pattern of changes in laboratory safety parameters (decreases in neutrophil and platelet counts, increases in ALT, AST and lipids), however, the magnitude of change and the frequency of marked abnormalities was higher with tocilizumab compared with adalimumab. Four (2.5%) patients in the tocilizumab arm and two (1.2%) patients in the adalimumab arm experienced CTC grade 3 or 4 neutrophil count decreases. Eleven (6.8%) patients in the tocilizumab arm and five (3.1%) patients in the adalimumab arm experienced ALT increases of CTC grade 2 or higher. The mean LDL increase from baseline was 0.64 mmol/L (25 mg/dL) for patients in the tocilizumab arm and 0.19 mmol/L (7 mg/dL) for patients in the adalimumab arm. The safety observed in the tocilizumab arm was consistent with the known safety profile of tocilizumab and no new or unexpected adverse reactions were observed (see Table 1).

5.2 Pharmacokinetic properties

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

RA patients

Intravenous use

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 3552 RA patients treated with a one-hour infusion of 4 or 8 mg/kg tocilizumab every 4 weeks for 24 weeks or with 162 mg tocilizumab given subcutaneously either once a week or every other week for 24 weeks.

The following parameters (predicted mean ± SD) were estimated for a dose of 8 mg/kg tocilizumab given every 4 weeks: steady-state area under curve (AUC) = 38000 ± 13000 h µg/mL, trough concentration (C_{min}) = 15.9 ± 13.1 µg/mL and maximum concentration (C_{max}) = 182 ± 50.4 µg/mL, and. the accumulation ratios for AUC and C_{max} were small, 1.32 and 1.09, respectively. The accumulation ratio was higher for C_{min} (2.49), which was expected based on the non-linear clearance contribution at lower concentrations. Steady-state was reached following the first administration for C_{max} and after 8 and 20 weeks for AUC and C_{min}, respectively. Tocilizumab AUC, C_{min} and C_{max} increased with increase of body weight. At body weight ≥ 100 kg, the predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 50000 ± 16800 µg•h/mL, 24.4 ± 17.5 µg/mL, and 226 ± 50.3 µg/mL, respectively, which are higher than mean exposure values for the patient population (i.e. all body weights) reported above. The dose-response curve for tocilizumab flattens at higher exposure, resulting in smaller efficacy gains for each incremental increase in concentration such that clinically meaningful increases in efficacy were not demonstrated in patients treated with > 800 mg of tocilizumab. Therefore, doses exceeding 800 mg per infusion are not recommended (see section 4.2).

Distribution

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

Elimination

Following intravenous administration, tocilizumab undergoes biphasic elimination from the circulation. The total clearance of tocilizumab was concentration-dependent and is the sum of the linear and non-linear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 9.5 mL/h. The concentration-dependent non-linear clearance plays a major role at low tocilizumab concentrations. Once the non-linear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.
The $t_{1/2}$ of tocilizumab was concentration-dependent. At steady-state following a dose of 8 mg/kg every 4 weeks, the effective $t_{1/2}$ decreased with decreasing concentrations within a dosing interval from 18 days to 6 days.

Linearity

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

Subcutaneous use

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

The pharmacokinetic parameters of tocilizumab did not change with time. For the 162 mg every week dose, the predicted mean (±SD) steady-state AUC1week, C_{min} and C_{max} of tocilizumab were 7970 ± 3432 µg•h/mL, 43.0 ± 19.8 µg/mL, and 49.8 ± 21.0 µg/mL, respectively. The accumulation ratios for AUC, C_{min}, and C_{max} were 6.32, 6.30, and 5.27, respectively. Steady-state was reached after 12 weeks for AUC, C_{min}, and C_{max}.

For the 162 mg every other week dose, the predicted mean (±SD) steady-state AUC2week, C_{min}, and C_{max} of tocilizumab were 3430 ± 2660 µg•h/mL, 5.7 ± 6.8 µg/mL, and 13.2 ± 8.8 µg/mL, respectively.

The accumulation ratios for AUC, C_{min}, and C_{max} were 2.67, 6.02, and 2.12, respectively. Steady-state was reached after 12 weeks for AUC and C_{min}, and after 10 weeks for C_{max}.

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

Elimination
For subcutaneous administration, the concentration-dependent apparent $t_{1/2}$ is up to 12 days for 162 mg every week and 5 days for 162 mg every other week in patients with RA at steady-state.

sJIA patients
Subcutaneous use
The pharmacokinetics of tocilizumab in sJIA patients was characterised by a population pharmacokinetic analysis which included 140 patients who were treated with 8 mg/kg intravenous every 2 weeks (patients weighing ≥30 kg), 12 mg/kg intravenous every 2 weeks (patients weighing below 30 kg), 162 mg subcutaneous every week (patients weighing ≥30 kg), 162 mg subcutaneous every 10 days or every 2 weeks (patients weighing below 30 kg).

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

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

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

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

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

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

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

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

pJIA patients

Subcutaneous use

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

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

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

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

After intravenous dosing, approximately 90% of the steady-state was reached by week 12 for the 10 mg/kg (body weight < 30 kg), and by week 16 for the 8 mg/kg (body weight ≥ 30 kg) dose. After subcutaneous dosing, approximately 90% of the steady-state was reached by week 12 for both the 162 mg subcutaneous Q2W and Q3W regimens.

Absorption

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

Distribution

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

Elimination

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

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

GCA patients

Subcutaneous use

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

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

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

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

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

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

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

Absorption
Following subcutaneous dosing in GCA patients, the absorption t½ was around 4 days. The bioavailability for the subcutaneous formulation was 0.8. 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
In GCA patients, the central volume of distribution was 4.09 L, the peripheral volume of distribution was 3.37 L, resulting in a volume of distribution at steady-state of 7.46 L.

Elimination
The total clearance of 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 6.7 mL/h in GCA patients,

In GCA patients, at steady-state, the effective t ½ 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 weekly regimen. At high serum concentrations, when total clearance of tocilizumab is dominated by linear clearance, an effective t ½ of approximately 32 days was derived from the population parameter estimates.

Special populations

Renal impairment

No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab has been conducted. Most of the patients in the RA and GCA studies population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (estimated creatinine clearance based on Cockcroft-Gault formula) did not impact the pharmacokinetics of tocilizumab .

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

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

Hepatic impairment

No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab has been conducted.

Age, gender and ethnicity

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

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

5.3 Preclinical safety data

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

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine (for pH-adjustment)
L-Histidine monohydrochloride monohydrate (for pH-adjustment)
L-Arginine/L-Arginine hydrochloride
L-Methionine
Polysorbate 80 (E 433)
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

3 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C). Do not freeze. Once removed from the refrigerator, the pre-filled pen can be stored up to 2 weeks at or below 30 °C.

Keep the pre-filled pen in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

0.9 mL solution in a pre-filled syringe (type I glass) with a staked-in needle containing 162 mg RoActemra assembled into a pre-filled pen. The syringe is closed by a rigid needle shield (elastomer seal with a polypropylene shell) and a plunger stopper (butyl rubber with a fluororesin coating).

Pack sizes of 4 pre-filled pens and multipacks containing 12 (3 packs of 4) pre-filled pens. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

RoActemra is supplied in a single use pre-filled pen. After removing the pre-filled pen from the refrigerator the pre-filled pen should be allowed to reach room temperature (18 °C to 28 °C) by waiting for 45 minutes, before injecting. The pen should not be shaken. After removing the cap the injection must be started within 3 minutes, to prevent the medicinal product from drying out and blocking the needle. If the pre-filled pen is not used within 3 minutes of removing the cap, you must dispose of it in a puncture resistant container and use a new pre-filled pen.

If following pressing the activation button the purple indicator does not move, you must dispose of the pre-filled pen in a puncture resistant container. **Do not** try to re-use the pre-filled pen. Do not repeat the injection with another pre-filled pen. Call your healthcare provider for help.

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

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

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/009
EU/1/08/492/010

9. DATE OF FIRST AUTHORISATION/DATE OF LATEST RENEWAL

Date of first authorisation: 16 January 2009
Date of last renewal: 25 September 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Lonza Manufacturing LLC
1000 New Horizons Way
Vacaville, CA
95688
United States

Genentech Inc.
1 Antibody Way
Oceanside, CA
92056
United States

Samsung Biologics Co Ltd
300, Songdo bio-daero, Yeonsu-gu
Incheon, 21987
Republic of Korea

Chugai Pharma Manufacturing Co., Ltd.
16-3 Kiyohara-Kogyodanchi
Utsunomiya City, Tochigi Pref., 321-3231
Japan

Novartis Singapore Pharmaceutical Manufacturing Pte. Ltd.
BioProduction Operations Singapore
8 Tuas Bay Lane
Singapore 636986
Singapore

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic safety update reports (PSURs)

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk management plan (RMP)**

The market authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall provide an educational pack covering the therapeutic indications RA, sJIA, pJIA and GCA, targeting all physicians who are expected to prescribe/use RoActemra containing the following:

- Physician Information Pack
- Nurse Information Pack
- Patient Information Pack

The MAH must agree the content and format of the educational material, together with a communication plan (including means of distribution), with the national competent authority prior to distribution of the educational material.

The Physician Information pack should contain the following key elements:

- Reference to the Summary of Product Characteristics (e.g., link to EMA website)
- Dose calculation (RA, sJIA and pJIA patients), preparation of infusion and infusion rate
- Risk of serious infections
    - The product must not be given to patients with active or suspected infection
    - The product may lessen signs and symptoms of acute infection delaying the diagnosis
- Risk of Hepatotoxicity
    - Caution should be exercised when considering initiation of tocilizumab treatment in patients with elevated transaminases ALT or AST above 1.5x ULN. In patients with elevated ALT or AST above 5x ULN treatment 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. The recommended dose modifications, including tocilizumab discontinuation, based on transaminases levels, in line with SmPC section 4.2.
- Risk of gastrointestinal perforations especially in patients with history of diverticulitis or intestinal ulcerations
- Details on how to report serious adverse drug reactions
- The Patient Information Packs (to be given to patients by healthcare professionals)
- Guidance on how to diagnose Macrophage Activation Syndrome in sJIA patients
- Recommendations for dose interruptions in sJIA and pJIA patients

The Nurse Information Pack should contain the following key elements:

- Prevention of medical errors and injection/infusion related reactions
    - Preparation of injection/infusion
    - Infusion rate
- Monitoring of the patient for injection/infusion related reactions
- Details on how to report serious adverse reactions

The Patient Information Pack should contain the following key elements:

- Package leaflet (with instructions for use for subcutaneous form) (e.g., link to EMA website)
- Patient Card

- to address the risk of getting infections which can become serious if not treated. In addition, some previous infections may reappear.
- to address the risk that patients using RoActemra may develop complications of diverticulitis which can become serious if not treated.
- to address the risk that patients using RoActemra may develop serious hepatic injury. Patients would be monitored for liver function tests. Patients should inform their doctor immediately if they experience signs and symptoms of liver toxicity including tiredness, abdominal pain and jaundice.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 20 mg/mL concentrate for solution for infusion
tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 80 mg tocilizumab.
1 vial contains 200 mg tocilizumab.
1 vial contains 400 mg tocilizumab.

3. LIST OF EXCIPIENTS

Also contains Polysorbate 80, sucrose, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
80 mg/4 mL
1 vial of 4 mL
4 vials of 4 mL

200 mg/10 mL
1 vial of 10 mL
4 vials of 10 mL

400 mg/20 mL
1 vial of 20 mL
4 vials of 20 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous infusion after dilution
The diluted product should be used immediately
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/001 1 vial of 4 mL
EU/1/08/492/002 4 vials of 4 mL
EU/1/08/492/003 1 vial of 10 mL
EU/1/08/492/004 4 vials of 10 mL
EU/1/08/492/005 1 vial of 20 mL
EU/1/08/492/006 4 vials of 20 mL

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

RoActemra 20 mg/mL sterile concentrate
tocilizumab
IV

2. METHOD OF ADMINISTRATION

IV infusion

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

80 mg/4 mL
200 mg/10 mL
400 mg/20 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 162 mg solution for injection in pre-filled syringe
tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe contains 162 mg tocilizumab.

3. LIST OF EXCIPIENTS

Also contains L-histidine, L-histidine monohydrochloride monohydrate, L-arginine/L-arginine hydrochloride, L-methionine, polysorbate 80, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
4 pre-filled syringes
Multipack: 12 (3 packs of 4) pre-filled syringes
162 mg/0.9 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Allow the syringe to sit at room temperature outside the box for 25 to 30 minutes before use

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Once removed from the refrigerator, the pre-filled syringe can be stored up to 2 weeks at or below 30 °C
Keep the pre-filled syringe in the outer carton in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/007 4 pre-filled syringes
EU/1/08/492/008 Multipack: 12 (3 packs of 4) pre-filled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

roactemra 162 mg syringe

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON (WITHOUT BLUE BOX) - Multipack

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 162 mg solution for injection in pre-filled syringe
tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe contains 162 mg tocilizumab.

3. LIST OF EXCIPIENTS

Also contains L-histidine, L-histidine monohydrochloride monohydrate, L-arginine/L-arginine hydrochloride, L-methionine, polysorbate 80, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
4 pre-filled syringes Component of a multipack, can't be sold separately
162 mg/0.9 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Allow the syringe to sit at room temperature outside the box for 25 to 30 minutes before use

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze

Once removed from the refrigerator, the pre-filled syringe can be stored up to 2 weeks at or below 30 °C
Keep the pre-filled syringe in the outer carton in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

roactemra 162 mg syringe

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

RoActemra 162 mg injection
tocilizumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

162 mg/0.9 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 162 mg solution for injection in pre-filled pen
tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled pen contains 162 mg tocilizumab.

3. LIST OF EXCIPIENTS

Also contains L-histidine, L-histidine monohydrochloride monohydrate, L-arginine/L-arginine hydrochloride, L-methionine, polysorbate 80, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
4 pre-filled pens ACTPen
Multipack: 12 (3 packs of 4) pre-filled pens ACTPen
162 mg/0.9 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Allow the pre-filled pen to sit at room temperature outside the box for 45 minutes before use

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Once removed from the refrigerator, the pre-filled pen can be stored up to 2 weeks at or below 30 °C
Keep the pre-filled pen in the outer carton in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/009 4 pre-filled pens
EU/1/08/492/010: 12 (3 packs of 4) pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

roactemra 162 mg pen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED PEN CARTON (WITHOUT BLUE BOX) - Multipack

1. NAME OF THE MEDICINAL PRODUCT

RoActemra 162 mg solution for injection in pre-filled pen

tocilizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled pen contains 162 mg tocilizumab.

3. LIST OF EXCIPIENTS

Also contains L-histidine, L-histidine monohydrochloride monohydrate, L-arginine/L-arginine hydrochloride, L-methionine, polysorbate 80, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
4 pre-filled pens ACTPen. Component of a multipack, can't be sold separately
162 mg/0.9 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Allow the pre-filled pen to sit at room temperature outside the box for 45 minutes before use

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Once removed from the refrigerator, the pre-filled pen can be stored up to 2 weeks at or below 30 °C
Keep the pre-filled pen in the outer carton in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

roactemra 162 mg pen

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

RoActemra 162 mg injection
tocilizumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

162 mg/0.9 mL

6. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

RoActemra 20 mg/mL concentrate for solution for infusion
tocilizumab

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

In addition to this leaflet, you will be given a **Patient Card**, which contains important safety information that you need to be aware of before and during treatment with RoActemra.

What is in this leaflet:

1. What RoActemra is and what it is used for

RoActemra contains the active substance tocilizumab, which is a protein made from specific immune cells (monoclonal antibody), that blocks the action of a specific protein (cytokine) called interleukin-6. This protein is involved in inflammatory processes of the body, and blocking it can reduce the inflammation in your body. RoActemra helps to reduce symptoms such as pain and swelling in your joints and can also improve your performance of daily tasks. RoActemra has been shown to slow the damage to the cartilage and bone of the joints caused by the disease and to improve your ability to do normal daily activities.

- **RoActemra is used to treat adults** with moderate to severe active rheumatoid arthritis (RA), an autoimmune disease, if previous therapies did not work well enough. RoActemra is usually given in combination with methotrexate. However, RoActemra can be given alone if your doctor determines that methotrexate is inappropriate.

- RoActemra can also be used to treat adults who have not had previous methotrexate treatment if they have severe, active and progressive rheumatoid arthritis.

- **RoActemra is used to treat children with sJIA**. RoActemra is used for children aged 2 years and over who have ***active systemic juvenile idiopathic arthritis*** (***sJIA***), an inflammatory disease that causes pain and swelling in one or more joints as well as fever and rash. RoActemra is used to improve the symptoms of sJIA and can be given in combination with methotrexate or alone.

- **RoActemra is used to treat children with pJIA**. RoActemra is used for children aged 2 years and over with active ***polyarticular juvenile idiopathic arthritis*** (***pJIA***), an inflammatory disease that causes pain and swelling in one or more joints. RoActemra is used to improve the symptoms of pJIA and can be given in combination with methotrexate or alone.

- **RoActemra is used to treat adults and children** aged 2 years and over with severe or life-threatening **cytokine release syndrome (CRS)**, a side-effect in patients treated with chimeric antigen receptor (CAR) T-cell therapies used to treat certain types of cancer.

- **RoActemra is used to treat adults** with coronavirus disease 2019 (COVID-19), receiving systemic corticosteroids and requiring supplemental oxygen or mechanical ventilation.

2. What you need to know before you are given RoActemra

You are not to be given RoActemra
- if you are **allergic** to tocilizumab or any of the other ingredients of this medicine (listed in Section 6).
- if you have an active, severe infection (with the exception of COVID-19).

If any of these applies to you, tell the doctor or nurse giving you the infusion.

Warnings and precautions
Talk to your doctor or nurse before you are given RoActemra.

- If you experience **allergic reactions** such as chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips or skin rash during or after the infusion, then **tell your doctor immediately.**

- If you have any kind of **infection**, short- or long-term, or if you often get infections. **Tell your doctor immediately** if you feel unwell. RoActemra can reduce your body's ability to respond to infections and may make an existing infection worse or increase the chance of getting a new infection.

- If you have had **tuberculosis**, tell your doctor. Your doctor will check for signs and symptoms of tuberculosis before starting RoActemra. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy tell your doctor immediately.

- If you have had **intestinal ulcers** or **diverticulitis**, tell your doctor. Symptoms would include abdominal pain and unexplained changes in bowel habits with a fever.

- If you have **liver disease**, tell your doctor. Before you use RoActemra, your doctor may do a blood test to measure your liver function.

- **If any patient has recently been vaccinated** (either adult or child), or is planning a vaccination, tell your doctor. All patients, especially children, should be up-to-date with all their vaccinations before they start treatment with RoActemra, unless urgent treatment initiation is required. Certain types of vaccines should not be used while receiving RoActemra.

- If you have **cancer**, tell your doctor. Your doctor will have to decide if you can still be given RoActemra.

- If you have **cardiovascular risk factors** such as raised blood pressure and raised cholesterol levels, tell your doctor. These factors need to be monitored while receiving RoActemra.

- If you have moderate to severe **kidney function problems**, your doctor will monitor you.

- If you have **persistent headaches**.

Your doctor will perform blood tests before you are given RoActemra, and during your treatment, to determine if you have a low white blood cell count, low platelet count or high liver enzymes.

Children and adolescents
RoActemra is not recommended for use in children under 2 years of age.

If a child has a history of ***macrophage activation syndrome***, (activation and uncontrolled proliferation of specific blood cells), tell your doctor. Your doctor will have to decide if they can still be given RoActemra.

Other medicines and RoActemra
Tell your doctor if you are taking any other medicines (or your child is, if they are the patient), or have recently taken any. This includes medicines obtained without a prescription. RoActemra can affect the way some medicines work, and the dose of these may require adjustment. If you are using medicines containing any of the following active substances, **tell your doctor**:

- methylprednisolone, dexamethasone, used to reduce **inflammation**
- simvastatin or atorvastatin, used to reduce **cholesterol levels**
- calcium channel blockers (e.g. amlodipine), used to treat **raised blood pressure**
- theophylline, used to treat **asthma**
- warfarin or phenprocoumon, used as a **blood thinning agents**
- phenytoin, used to treat **convulsions**
- ciclosporin, used to **suppress your immune system** during organ transplants
- benzodiazepines (e.g. temazepam), used to **relieve anxiety.**

Due to lack of clinical experience, RoActemra is not recommended for use with other biological medicines for the treatment of RA, sJIA or pJIA.

Pregnancy, breast-feeding and fertility
RoActemra is not to be used in pregnancy unless clearly necessary. Talk to your doctor if you are pregnant, may be pregnant, or intend to become pregnant.

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

Stop breast-feeding if you are to be given RoActemra, and talk to your doctor. Leave a gap of at least 3 months after your last treatment before you start breast-feeding. It is not known whether RoActemra is passed into breast milk.

The data available so far does not suggest any effect on fertility from this treatment.

Driving and using machines
This medicine can cause dizziness. If you feel dizzy, do not drive or use machines.

RoActemra contains sodium
After dilution with 0.9% sodium chloride solution, this medicinal product contains 230.6 mg sodium per maximum dose of 800 mg equivalent to 11.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

RoActemra contains polysorbate
This medicine contains 5 mg of polysorbate 80 in each 200 mg/10 mL vial, 10 mg of polysorbate 80 in each 400 mg/20 mL vial, and 2 mg of polysorbate 80 in each 80 mg/4 mL vial, which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have or your child has any known allergies.

3. How RoActemra is given

This medicine is subject to restricted medical prescription by your doctor.

RoActemra will be given to **you as a drip into a vein, by a doctor or a nurse.** They will dilute the solution, set up the intravenous infusion and monitor you during and after the treatment.

Adult patients with RA
The usual dose of RoActemra is 8 mg per kg of body weight. Depending on your response, your doctor may decrease your dose to 4 mg/kg then increase back to 8 mg/kg when appropriate.

Adults will be given RoActemra once every 4 weeks through a drip in the vein (intravenous infusion) over one hour.

Children with sJIA (aged 2 and over)
The usual dose of RoActemra depends on your weight.
- If you weigh less than 30 kg: the dose is **12 mg for every kilogram of body weight**
- If you weigh 30 kg or more: the dose is **8 mg for every kilogram of body weight**

The dose is calculated based on your body weight at each administration.

Children with sJIA will be given RoActemra once every 2 weeks through a drip in the vein (intravenous infusion) over one hour.

Children with pJIA (aged 2 and over)
The usual dose of RoActemra depends on your weight.
- If you weigh less than 30 kg: the dose is **10 mg for every kilogram of body weight**
- If you weigh 30 kg or more: the dose is **8 mg for every kilogram of body weight**

The dose is calculated based on your body weight at each administration.

Children with pJIA will be given RoActemra once every 4 weeks through a drip in the vein (intravenous infusion) over one hour.

Patients with CRS
The usual dose of RoActemra is **8 mg for every kg of body weight if you weigh 30 kg or more**.
The dose is **12 mg for every kg of body weight if you weigh less than 30 kg**.
RoActemra can be given alone or in combination with corticosteroids.

Patients with COVID-19
The usual dose of RoActemra is **8 mg for every kg of body weight.** A second dose may be required.

If you are given more RoActemra than you should
Since RoActemra is given by a doctor or nurse, it is unlikely that you will be given too much. However, if you are worried, talk to your doctor.

If you miss a dose of RoActemra
Since RoActemra is given by a doctor or nurse, it is unlikely that you will miss a dose. However, if you are worried, talk to your doctor or nurse.

If you stop being given RoActemra
You should not stop using RoActemra without discussing with your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, RoActemra can cause side effects, although not everybody gets them. Side effects could occur at least up to 3 months after your last dose of RoActemra.

Possible serious side effects
Tell your doctor **immediately** if you experience any of the following side effects:

These are common: may affect up to 1 in 10 people

Allergic reactions during or after infusion:
- difficulty with breathing, chest tightness or light-headedness
- rash, itching, hives, swelling of the lips, tongue or face

Signs of serious infections:
- fever and chills
- mouth or skin blisters
- stomach ache

Signs and symptoms of liver toxicity:
These are rare: may affect up to 1 in 1 000 people
- tiredness
- abdominal pain
- jaundice (yellow discolouration of skin or eyes)

List of other possible side effects
If you notice any of these, tell your doctor **as soon as possible:**

Very common side effects:
These may affect more than 1 in 10 people
- upper respiratory tract infections with typical symptoms such as cough, blocked nose, runny nose, sore throat and headache
- high blood fat (cholesterol) levels

Common side effects:
These may affect up to 1 in 10 people
- lung infection (pneumonia)
- shingles (herpes zoster)
- cold sores (oral herpes simplex), blisters
- skin infection (cellulitis) sometimes with fever and chills
- rash and itching, hives
- allergic (hypersensitivity) reactions
- eye infection (conjunctivitis)
- headache, dizziness, high blood pressure
- mouth ulcers, stomach pain
- fluid retention (oedema) in the lower legs, weight increase
- cough, shortness of breath
- low white blood cell counts shown by blood tests (neutropenia, leucopenia)
- abnormal liver function tests (increased transaminases)
- increased bilirubin shown by blood tests
- low fibrinogen levels in the blood (a protein involved in blood clotting)

Uncommon side effects:
These may affect up to 1 in 100 people
- diverticulitis (fever, nausea, diarrhoea, constipation, stomach pain)
- red swollen areas in the mouth
- high blood fat (triglycerides)
- stomach ulcer
- kidney stones
- underactive thyroid

Rare side effects:

These may affect up to 1 in 1 000 people
- Stevens-Johnson syndrome (skin rash, which may lead to severe blistering and peeling of the skin)
- fatal allergic reactions (anaphylaxis)
- inflammation of the liver (hepatitis), jaundice

Very rare side effects:
These may affect up to 1 in 10 000 people
- low counts for white blood cells, red blood cells and platelets in blood tests
- liver failure

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

Children with sJIA
In general, side effects in sJIA patients were of a similar type to those in adults with RA. Some side effects were seen more often: inflamed nose and throat, diarrhoea, lower white blood cell counts and higher liver enzymes.

Children with pJIA
In general, side effects in pJIA patients were of a similar type to those in adults with RA. Some side effects were seen more often: inflamed nose and throat, headache, feeling sick (nausea) and lower white blood cell counts.

5. How to store RoActemra

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

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

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

6. Contents of the pack and other information

What RoActemra contains
- The active substance is tocilizumab.
  Each 4 mL vial contains 80 mg tocilizumab (20 mg/mL).
  Each 10 mL vial contains 200 mg tocilizumab (20 mg/mL).
  Each 20 mL vial contains 400 mg tocilizumab (20 mg/mL).

- The other ingredients are sucrose, polysorbate 80, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate and water for injections (see section 2 ‘RoActemra contains sodium’ and ‘RoActemra contains polysorbate’).

What RoActemra looks like and contents of the pack
RoActemra is a concentrate for solution for infusion. The concentrate is a clear to opalescent, colourless to pale yellow liquid.
RoActemra is supplied as vials containing 4 mL, 10 mL and 20 mL concentrate for solution for infusion. Pack size of 1 and 4 vials. Not all pack sizes may be marketed.

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Instructions for dilution prior to administration
Parenteral medicinal products must be inspected visually for particulate matter or discolouration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted. Use a sterile needle and syringe to prepare RoActemra.

RA, COVID-19 and CRS adult patients (≥ 30 kg)
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 100 mL infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.4 mL/kg**) should be withdrawn from the vial and placed in the 100 mL infusion bag. This should be a final volume of 100 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

Use in the paediatric population

sJIA, pJIA and CRS patients ≥ 30 kg
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 100 mL infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.4 mL/kg**) should be withdrawn from the vial and placed in the 100 mL infusion bag. This should be a final volume of 100 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

sJIA and CRS patients < 30 kg
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 50 mL infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.6 mL/kg**) should be withdrawn from the vial and placed in the 50 mL infusion bag. This should be a final volume of 50 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

pJIA patients < 30 kg
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 50 mL infusion bag, equal to the volume of RoActemra concentrate required for the patients dose, under aseptic conditions. The required amount of RoActemra concentrate (**0.5 mL/kg**) should be withdrawn from the vial and placed in the 50 mL infusion bag. This should be a final volume of 50 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

RoActemra is for single-use only.

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

Package leaflet: Information for the user

RoActemra 162 mg solution for injection in pre-filled syringe
tocilizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it onto others. It may harm them even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

In addition to this leaflet, you will be given a **Patient Card**, which contains important safety information that you need to be aware of before and during treatment with RoActemra.

What is in this leaflet:

1. What RoActemra is and what it is used for

RoActemra contains the active substance tocilizumab, which is a protein made from specific immune cells (monoclonal antibody), that blocks the action of a specific protein (cytokine) called interleukin-6. This protein is involved in inflammatory processes of the body, and blocking it can reduce the inflammation in your body. RoActemra is used to treat:

- **adults with moderate to severe active rheumatoid arthritis (RA)**, an autoimmune disease, if previous therapies did not work well enough.

- **adults with severe, active and progressive rheumatoid arthritis (RA),** who have not had previous treatment with methotrexate.

  RoActemra helps to reduce RA symptoms such as pain and swelling in your joints, and can also improve your performance of daily tasks. RoActemra has been shown to slow the damage to the cartilage and bone of the joints caused by the disease and to improve your ability to do normal daily activities.

  RoActemra is usually given in combination with another medicine for RA called methotrexate. However, RoActemra can be given alone if your doctor determines that methotrexate is inappropriate.

- **adults with a disease of the arteries called giant cell arteritis** (**GCA**), caused by inflammation of the body's largest arteries, especially those that supply blood to the head and neck. Symptoms include headache, fatigue and jaw pain. Effects can include strokes and blindness.

RoActemra can reduce pain and swelling in the arteries and veins in your head, neck and arms.

GCA is often treated with medicines called steroids. They are usually effective, but can have side effects if used at high doses for a long time. Reducing the steroid dose can also lead to a flare-up of the GCA. Adding RoActemra to the treatment means that steroids can be used for a shorter time, while still controlling GCA.

- **children and adolescents, aged 1 year and over, with active *systemic juvenile idiopathic arthritis (sJIA)*,** an inflammatory disease that causes pain and swelling in one or more joints as well as fever and rash.

  RoActemra is used to improve the symptoms of sJIA. It can be given in combination with methotrexate or alone.

- **children and adolescents, aged 2 years and over, with active *polyarticular juvenile idiopathic arthritis* (*pJIA*).** This is an inflammatory disease that causes pain and swelling in one or more joints.

  RoActemra is used to improve the symptoms of pJIA. It can be given in combination with methotrexate or alone**.**

2. What you need to know before you use RoActemra

Do not use RoActemra
- if you or a child patient you look after are allergic to tocilizumab or any of the other ingredients of this medicine (listed in section 6).
- if you or a child patient you look after have an active, severe infection.

If either of these applies to you, tell a doctor. Do not use RoActemra.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using RoActemra.

- If you experience **allergic reactions** such as chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips, tongue, face or skin itching, hives or rash during or after the injection, then **tell your doctor immediately.**

- Do not take the next dose until you have informed your doctor AND your doctor has told you to take the next dose if you have experienced any allergic reaction symptoms after RoActemra administration.
- If you have any kind of **infection**, short- or long-term, or if you often get infections. **Tell your doctor immediately** if you feel unwell. RoActemra can reduce your body's ability to respond to infections and may make an existing infection worse or increase the chance of getting a new infection.

- If you have had **tuberculosis**, tell your doctor. Your doctor will check for signs and symptoms of tuberculosis before starting RoActemra. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever) or any other infection appear during or after therapy tell your doctor immediately.

- If you have had **intestinal ulcers** or **diverticulitis**, tell your doctor. Symptoms would include abdominal pain and unexplained changes in bowel habits with a fever.

- If you have **liver disease**, tell your doctor. Before you use RoActemra, your doctor may do a blood test to measure your liver function.

- **If any patient has recently been vaccinated,** or is planning a vaccination**,** tell your doctor. All patients should be up-to-date with all their vaccinations before they start treatment with RoActemra. Certain types of vaccines should not be given while receiving RoActemra.

- If you have **cancer**, tell your doctor. Your doctor will have to decide if you can still be given RoActemra.

- If you have **cardiovascular risk factors** such as raised blood pressure and raised cholesterol levels, tell your doctor. These factors need to be monitored while receiving RoActemra.

- If you have moderate to severe **kidney function problems**, your doctor will monitor you.

- If you have **persistent headaches**.

Your doctor will perform a blood test before you receive RoActemra, to determine if you have a low white blood cell count, low platelet count or high liver enzymes.

Children and adolescents
RoActemra subcutaneous injection is not recommended for use in children under 1 year of age. RoActemra must not be given to children with sJIA weighing less than 10 kg.

If a child has a history of ***macrophage activation syndrome*** (activation and uncontrolled proliferation of specific blood cells), tell your doctor. Your doctor will have to decide if they can still be given RoActemra.

Other medicines and RoActemra
Tell your doctor if you are taking any other medicines, or have recently taken any. RoActemra can affect the way some medicines work, and the dose of these may require adjustment. If you are using medicines containing any of the following active substances, **tell your doctor:**
- methylprednisolone, dexamethasone, used to reduce inflammation
- simvastatin or atorvastatin, used to reduce cholesterol levels
- calcium channel blockers (e.g. amlodipine), used to treat raised blood pressure
- theophylline, used to treat asthma
- warfarin or phenprocoumon, used as a blood thinning agents
- phenytoin, used to treat convulsions
- ciclosporin, used to suppress your immune system during organ transplants
- benzodiazepines (e.g. temazepam), used to relieve anxiety

Due to lack of clinical experience, RoActemra is not recommended for use with other biological medicines for the treatment of RA, sJIA, pJIA or GCA.

Pregnancy, breast-feeding and fertility

RoActemra is not to be used in pregnancy unless clearly necessary. Talk to your doctor if you are pregnant, may be pregnant, or intend to become pregnant.

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

Stop breast-feeding if you are to be given RoActemra, and talk to your doctor. Leave a gap of at least 3 months after your last treatment before you start breast-feeding. It is not known whether RoActemra is passed into breast milk.

Driving and using machines
This medicine can cause dizziness. If you feel dizzy, do not drive or use machines.

RoActemra contains polysorbate
This medicine contains 0.18 mg of polysorbate 80 in each 162 mg/0.9 mL PFS which is equivalent to 0.2 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have or your child has any known allergies.

3. How to use RoActemra

Always use this medicine exactly as your doctor, pharmacist or nurse has told you. You should check with your doctor, pharmacist or nurse if you are not sure.

The treatment will be prescribed and started by healthcare professionals experienced in the diagnosis and treatment of RA, sJIA, pJIA or GCA.

The recommended dose
The dose for RA and GCA adults is 162 mg (the content of 1 pre-filled syringe) given once a week.

Children and adolescents with sJIA (aged 1 year and over)
The usual dose of RoActemra depends on the patient's weight.
- If the patient weighs **less than 30 kg**: the dose is 162 mg (the content of 1 pre-filled syringe) once every 2 weeks
- If the patient weighs **30 kg or more**: the dose is 162 mg (the content of 1 pre-filled syringe) once every week

Children and adolescents with pJIA (aged 2 and over)
The usual dose of RoActemra depends on the patient's weight.
- If the patient weighs **less than 30 kg**: the dose is 162 mg (the content of 1 pre-filled syringe), **once every 3 weeks**
- If the patient weighs **30 kg or more**: the dose is 162 mg (the content of 1 pre-filled syringe), **once every 2 weeks.**

RoActemra is given by injection under the skin (*subcutaneously*). At the start, your doctor or nurse may inject RoActemra. However, your doctor may decide that you may inject RoActemra yourself. In this case you will get training on how to inject RoActemra yourself. Parents and carers will get training on how to inject RoActemra for patients who cannot inject themselves, such as children.

Talk to your doctor if you have any questions about giving yourself or a child patient you look after an injection. You will find detailed "Instructions for administration" at the end of this leaflet.

If you use more RoActemra than you should
Because RoActemra is given in one pre-filled syringe, it is unlikely that you will receive too much. However, if you are worried, talk to your doctor, pharmacist or nurse.

If an adult with RA or GCA or a child or adolescent with sJIA misses or forgets a dose
It is very important to use RoActemra exactly as prescribed by your doctor. Keep track of your next dose.
- If you miss your weekly dose within 7 days, take your dose on the next scheduled day.
- If you miss your once every 2 weeks dose within 7 days, inject a dose as soon as you remember and take your next dose at your regular scheduled time.
- If you miss your dose by more than 7 days, or you are not sure when to inject RoActemra, call your doctor or pharmacist.

If a child or adolescent with pJIA misses or forgets a dose
It is very important to use RoActemra exactly as prescribed by the doctor. Keep track of the next dose.
- If a dose is missed within 7 days, inject a dose as soon as you remember and give the next dose at the regular scheduled time.
- If a dose is missed by more than 7 days, or you are not sure when to inject RoActemra, call the doctor or pharmacist.

If you stop using RoActemra
You should not stop using RoActemra without discussing with your doctor first.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, RoActemra can cause side effects, although not everybody gets them.
Side effects could occur 3 months or more after your last dose of RoActemra.

Possible serious side effects
Tell your doctor **immediately** if you experience any of the following side effects:

These are common: they may affect up to 1 in every 10 people
Allergic reactions during or after injection:
- difficulty with breathing, chest tightness or light-headedness
- rash, itching, hives, swelling of the lips, tongue or face

Signs of serious infections:
- fever and chills
- mouth or skin blisters
- stomach ache

Signs and symptoms of liver toxicity:
These are rare: may affect up to 1 in 1 000 people
- tiredness
- abdominal pain
- jaundice (yellow discolouration of skin or eyes)

List of other possible side effects
If you notice any of these, tell your doctor **as soon as possible**:

Very common side effects:
These may affect 1 in 10 people or more
- upper respiratory tract infections with typical symptoms such as cough, blocked nose, runny nose, sore throat and headache
- high blood fat (*cholesterol*) levels
- injection site reactions

Common side effects:
These may affect up to 1 in 10 people
- lung infection (pneumonia)
- shingles (herpes zoster)
- cold sores (oral herpes simplex), blisters
- skin infection (cellulitis) sometimes with fever and chills
- rash and itching, hives
- allergic (hypersensitivity) reactions

- eye infection (conjunctivitis)
- headache, dizziness, high blood pressure
- mouth ulceration, stomach pain
- fluid retention (oedema) in the lower legs, weight increase
- cough, shortness of breath
- low white blood cell counts shown by blood tests (neutropenia, leucopenia)
- abnormal liver function tests (increased transaminases)
- increased bilirubin shown by blood tests
- low fibrinogen levels in the blood (a protein involved in blood clotting)

Uncommon side effects:
These may affect up to 1 in every 100 people
- diverticulitis (fever, nausea, diarrhoea, constipation, stomach pain)
- red swollen areas in the mouth
- high blood fat (triglycerides)
- stomach ulcer
- kidney stones
- underactive thyroid

Rare side effects:
These may affect up to 1 in every 1 000 people
- Stevens-Johnson syndrome (skin rash, which may lead to severe blistering and peeling of the skin)
- fatal allergic reactions (anaphylaxis)
- inflammation of the liver (hepatitis), jaundice

Very rare side effects:
These may affect up to 1 in every 10 000 people
- low counts for white blood cells, red blood cells and platelets in blood tests
- liver failure

Side effects in children and adolescents with sJIA or pJIA
Side effects in children and adolescents with sJIA or pJIA are generally similar to those in adults. Some side effects are seen more often in children and adolescents: inflamed nose and throat, headache, feeling sick (nausea) and lower white blood cell counts.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store RoActemra

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pre-filled syringe label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze. Once removed from the refrigerator, the pre-filled syringe can be stored up to 2 weeks at or below 30 °C.

Keep the pre-filled syringes in the outer carton in order to protect from light and moisture.

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

The syringe should not be shaken. After removing the cap the injection must be started within 5 minutes to prevent the medicine from drying out and blocking the needle. If the pre-filled syringe is not used within 5 minutes of cap removal, you must dispose of it in a puncture resistant container and use a new pre-filled syringe.

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

6. Contents of the pack and other information

What RoActemra contains

- The active substance is tocilizumab.

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

- The other ingredients are L-Histidine, L-Histidine monohydrochloride monohydrate, L-Arginine/L-Arginine hydrochloride, L-Methionine, Polysorbate 80 and Water for injections (see section 2 ‘RoActemra contains polysorbate’).

What RoActemra looks like and contents of the pack

RoActemra is a solution for injection. The solution is colourless to slightly yellowish.
RoActemra is supplied as a 0.9 mL pre-filled syringe containing 162 mg tocilizumab solution for injection. Each pack contains 4 pre-filled syringes with multipacks containing 12 (3 packs of 4) pre-filled syringes. Not all pack sizes may be marketed.

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu.

What do I need to know to use my RoActemra pre-filled syringe safely?

It is important to read, understand and follow these instructions so that you or your caregiver uses the RoActemra syringe correctly. These instructions do not replace training from your healthcare provider. Your healthcare provider should show you how to prepare and inject properly before you use the RoActemra syringe for the first time. Ask your healthcare provider any questions you may have. Do not attempt to administer an injection until you are sure that you understand how to use the RoActemra syringe.

Please also read the Patient Leaflet that comes with the RoActemra syringe for the most important information you need to know about the medicine. It is important to remain under your healthcare provider's care while using RoActemra.

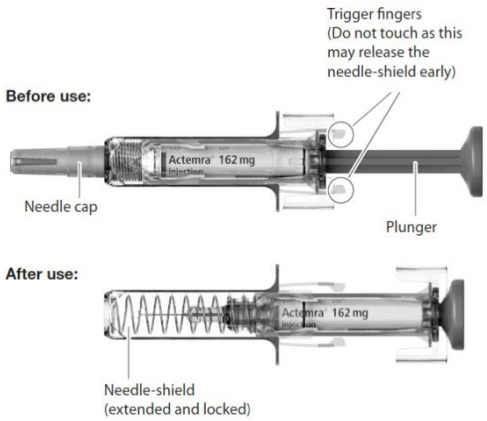
Important Information:

- Do not use the syringe if it appears to be damaged
- Do not use if medicine is cloudy, hazy, discoloured or contains particles
- Do not try to take apart the syringe at any time
- Do not remove the needle-cap until you are ready to inject
- Do not inject through clothing covering the skin
- Never re-use the same syringe
- Do not touch the syringe trigger fingers as this may damage the syringe

Storage

Keep the RoActemra syringe and all medicines out of the sight and reach of children. Always store the syringe in a refrigerator at a temperature of 2 °C – 8 °C. Once removed from the refrigerator, the pre-filled syringe can be stored for a total time of up to 2 weeks at or below 30 °C, but not exceeding the original expiry date (EXP). Mark the relevant date on the carton. The prefilled syringe must always be kept in the carton. Protect the syringe from freezing and from light. Keep the syringes dry.

Pre-filled syringe parts



You will need the following to give your injection:
Included in the box:
Pre-filled Syringe

Not included in the box:
- Alcohol pad
- Sterile cotton ball or gauze
- Puncture-resistant container or sharps container for safe disposal of needle-cap and used syringe

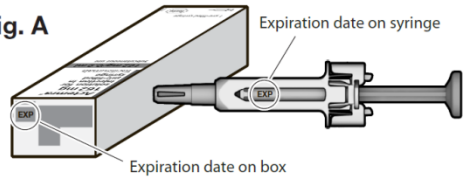
A place to prepare your supplies:

- **Find a well-lit, clean, flat surface such as a table**

Step 1. Visually check the syringe

- Take the box containing the syringe out of the refrigerator and open the box. Do not touch the trigger fingers on the syringe as this may damage the syringe.
- Remove the syringe from the box and visually examine the syringe, as well as the medicine in the syringe. This is important to ensure that the syringe and medicine are safe to use.
- Check the expiry date on the box and syringe (See Fig. A) to make sure that it has not passed (expired). Do not use the syringe if the expiry date has passed. This is important to ensure that the syringe and medicine are safe to use.

Fig. A



Dispose of the syringe and do not use if:

- the medicine is cloudy
- the medicine contains particles
- the medicine is any colour besides colourless to yellowish
- any part of the syringe appears to be damaged

Step 2. Allow the syringe to adjust to room temperature

- Do not remove the needle-cap on your syringe until Step 5. Early removal of the needle-cap can cause the medication to dry out and block the needle.

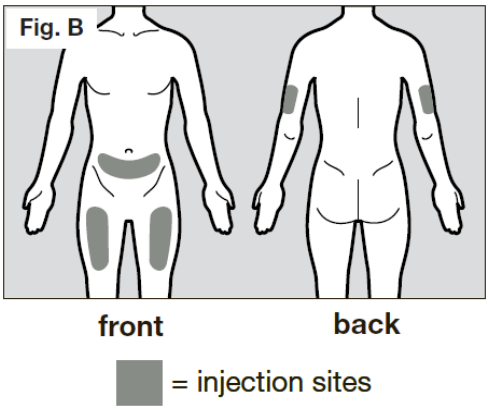
- Place the syringe on a clean flat surface and allow the syringe to come to room temperature (18 °C - 28 °C) for about 25-30 minutes to warm up. Not allowing the syringe to come to room temperature could result in an uncomfortable injection and it may be difficult to depress the plunger.
- Do not warm up the syringe in any other way.

Step 3. Clean your hands

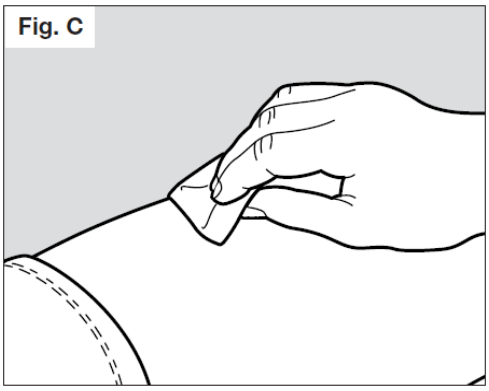
- Wash your hands with soap and water.

Step 4. Choose and prepare an injection site

- The recommended injection sites are the front and middle of your thighs and the lower part of the abdomen below the navel (belly button) except for the five centimeter area directly around the navel. (See Fig. B)
- If a caregiver is giving the injection, the outer area of the upper arms may also be used. (See Fig. B)



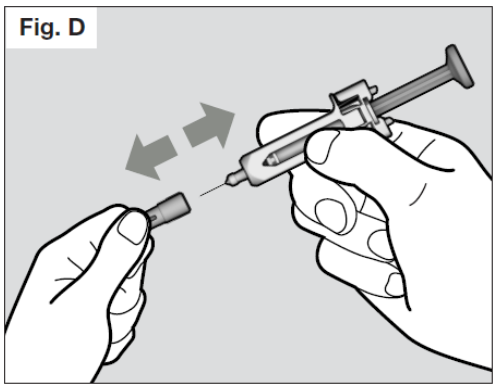
- You should use a different place each time you give yourself an injection, at least three centimeters from the area you used for your previous injection.
- Do not inject into areas that could be bothered by a belt or waistband. Do not inject into moles, scars, bruises, or areas where the skin is tender, red, hard or not intact.
- Clean the chosen injection site area using the alcohol pad (See Fig. C), to reduce the risk of infection.



- Let the skin dry for approximately 10 seconds.
- Be sure not to touch the cleaned area prior to the injection. Do not fan or blow on the clean area.

Step 5. Remove needle-cap

- Do not hold the syringe by the plunger while removing the needle-cap.
- Hold the needle-shield of the syringe firmly with one hand and pull off the needle-cap with the other hand. (See Fig. D) If you cannot remove the needle cap you should request the help of a caregiver or contact your healthcare provider.



- Do not touch the needle or let it touch any surface.
- There may be a small air bubble in the RoActemra prefilled syringe. You do not need to remove it.
- You may see a drop of liquid at the end of the needle. This is normal.
- Throw away the needle-cap in the puncture resistant container or sharps container.

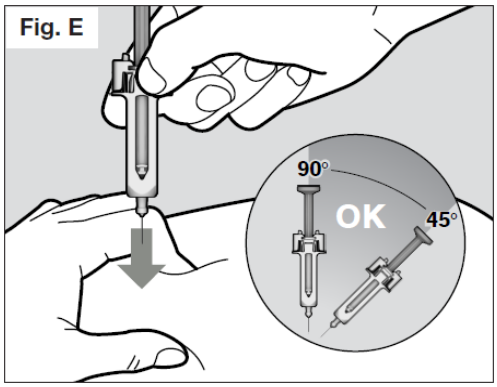
NOTE: Once the needle-cap is removed, the syringe must be used immediately.

- If it is not used within 5 minutes of cap removal, the syringe must be disposed of in the puncture resistant container or sharps container and a new syringe must be used. If the needle cap is removed for more than 5 minutes, it may be more difficult to perform an injection as the medicine can dry out and block the needle.

- Never reattach the needle-cap after removal.

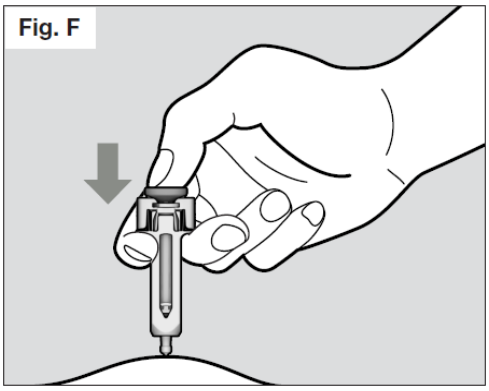
Step 6. Give the injection

- Hold the syringe comfortably in your hand.
- To be sure the needle can be inserted correctly under the skin, pinch a fold of loose skin at the clean injection site with your free hand. Pinching the skin is important to ensure that you inject under the skin (into fatty tissue) but not any deeper (into muscle). Injection into muscle could result in an uncomfortable injection.
- Do not hold or push on the plunger while inserting the needle into the skin.
- Insert the needle all the way into the pinched skin at an angle between 45° to 90° with a quick, firm action. (See Fig. E).

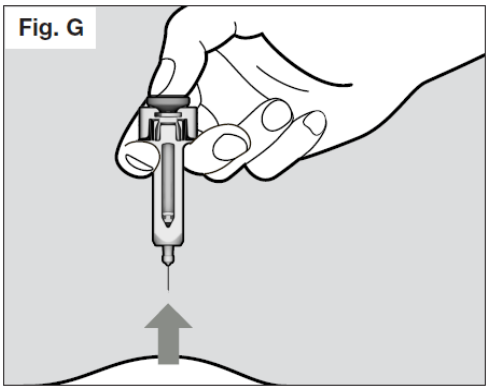


It is important to choose the correct angle to ensure the medication is delivered under the skin (into fatty tissue), otherwise the injection could be painful and the medication may not work.

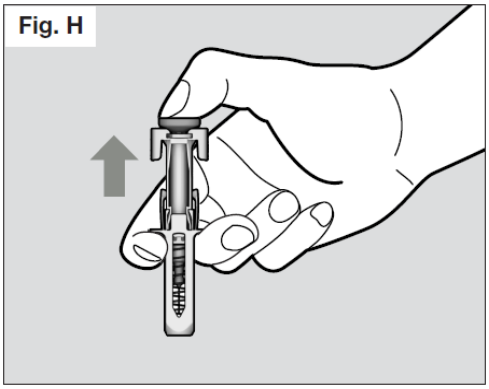
- Then keep the syringe in position and let go of the pinch of skin.
- Slowly inject all of the medicine by gently pushing the plunger all the way down. (See Fig. F). You must press the plunger all the way down to ensure that you get the full dose of medication and to ensure the trigger fingers are completely pushed to the side. If the plunger is not fully depressed the needle shield will not extend to cover the needle when it is removed. If the needle is not covered proceed carefully, and place the syringe into the puncture resistant container to avoid injury with the needle.



• Once the plunger is pushed all the way down, keep pressing down on the plunger to be sure all of the medicine is injected before taking the needle out of the skin.
• Keep pressing down on the plunger while you take the needle out of the skin at the same angle as inserted. (See Fig. G)
• If following insertion of the needle, you cannot press down the plunger, you must dispose of the pre-filled syringe in a puncture resistant container and use a new pre-filled syringe (starting again at Step 2). If you still experience difficulty, you should consult your healthcare provider.



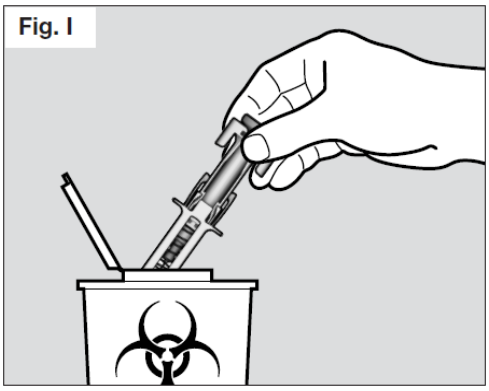
• Once the needle is removed completely from the skin, you can release the plunger, allowing the needle-shield to protect the needle. (See Fig. H)



• If you see drops of blood at the injection site, you can press a sterile cotton ball or gauze over the injection site for approximately 10 seconds.
• Do not rub the injection site.

Step 7. Dispose of the syringe

- Do not try to re-cap your syringe.
- Throw away used syringes in a puncture-resistant container or sharps container. Ask your healthcare provider or pharmacist for information about where you can get a "sharps" container or what other types of puncture-resistant containers you can use to safely dispose of your used syringes, if you do not have one. (See Fig. I)



Check with your healthcare provider for instructions about the right way to throw away used syringes. There may be local or state laws about how to throw away used syringes.

Do not throw away used syringes or the puncture resistant container in household trash and do not recycle them.

- Dispose of the full container as instructed by your healthcare provider or pharmacist.
- Always keep the puncture-resistant container out of the sight and reach of children.

Patient advice regarding hypersensitivity reactions (also known as anaphylaxis, if severe)

If you develop symptoms such as, but not limited to skin rash, itching, chills, swelling of face, lips, tongue or throat, chest pain, wheezing, difficulty breathing or swallowing or feeling dizzy or faint at any time while not at the clinic during or following an RoActemra injection you should seek emergency care immediately.

Patient advice regarding early recognition and treatment to limit risk of a serious infection

Be alert for the first signs of infection such as:

- body aches, fever, chills
- cough, chest discomfort/tightness, shortness of breath
- redness, heat, unusual swelling of skin or joint
- abdominal pain/tenderness and/or change in bowel function

Call your doctor and seek medical attention without delay if you think you might be developing an infection.

If you have any concerns or questions about your syringe, contact your healthcare provider or pharmacist for assistance.

Package leaflet: Information for the user

RoActemra 162 mg solution for injection in pre-filled pen
tocilizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it onto others. It may harm them even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

In addition to this leaflet, you will be given a **Patient Card**, which contains important safety information that you need to be aware of before and during treatment with RoActemra.

What is in this leaflet:

1. What RoActemra is and what it is used for

RoActemra contains the active substance tocilizumab, which is a protein made from specific immune cells (monoclonal antibody), that blocks the action of a specific protein (cytokine) called interleukin-6. This protein is involved in inflammatory processes of the body, and blocking it can reduce the inflammation in your body. RoActemra is used to treat:

- **adults with moderate to severe active rheumatoid arthritis (RA)**, an autoimmune disease, if previous therapies did not work well enough.

- **adults with severe, active and progressive rheumatoid arthritis (RA),** who have not had previous treatment with methotrexate.

  RoActemra helps to reduce symptoms such as pain and swelling in your joints and can also improve your performance of daily tasks. RoActemra has been shown to slow the damage to the cartilage and bone of the joints caused by the disease and to improve your ability to do normal daily activities.

  RoActemra is usually given in combination with another medicine for RA called methotrexate. However, RoActemra can be given alone if your doctor determines that methotrexate is inappropriate.

- **adults with a disease of the arteries called giant cell arteritis** (**GCA**), caused by inflammation of the body's largest arteries, especially those that supply blood to the head and neck. Symptoms include headache, fatigue and jaw pain. Effects can include strokes and blindness.

RoActemra can reduce pain and swelling in the arteries and veins in your head, neck and arms.

GCA is often treated with medicines called steroids. They are usually effective, but can have side effects if used at high doses for a long time. Reducing the steroid dose can also lead to a flare-up of the GCA. Adding RoActemra to the treatment means that steroids can be used for a shorter time, while still controlling GCA.

- **children and adolescents, aged 12 years and over, with active *systemic juvenile idiopathic arthritis (sJIA)*,** an inflammatory disease that causes pain and swelling in one or more joints as well as fever and rash.

  RoActemra is used to improve the symptoms of sJIA. It can be given in combination with methotrexate or alone.

- **children and adolescents, aged 12 years and over, with active *polyarticular juvenile idiopathic arthritis* (*pJIA*).** This is an inflammatory disease that causes pain and swelling in one or more joints.

  RoActemra is used to improve the symptoms of pJIA. It can be given in combination with methotrexate or alone**.**

2. What you need to know before you use RoActemra

Do not use RoActemra

- if you or a child patient you look after are allergic to tocilizumab or any of the other ingredients of this medicine (listed in section 6).
- if you or a child patient you look after have an active, severe infection.

If either of these applies to you, tell a doctor. Do not use RoActemra.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using RoActemra.

- If you experience **allergic reactions** such as chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips, tongue, face or skin itching, hives or rash during or after the injection, then **tell your doctor immediately.**

- Do not take the next dose until you have informed your doctor AND your doctor has told you to take the next dose if you have experienced any allergic reaction symptoms after RoActemra administration.

- If you have any kind of **infection**, short- or long-term, or if you often get infections. **Tell your doctor immediately** if you feel unwell. RoActemra can reduce your body’s ability to respond to infections and may make an existing infection worse or increase the chance of getting a new infection.

- If you have had **tuberculosis**, tell your doctor. Your doctor will check for signs and symptoms of tuberculosis before starting RoActemra. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever) or any other infection appear during or after therapy tell your doctor immediately.

- If you have had **intestinal ulcers** or **diverticulitis**, tell your doctor. Symptoms would include abdominal pain and unexplained changes in bowel habits with a fever.

- If you have **liver disease**, tell your doctor. Before you use RoActemra, your doctor may do a blood test to measure your liver function.

- **If any patient has recently been vaccinated,** or is planning a vaccination**,** tell your doctor. All patients should be up-to-date with all their vaccinations before they start treatment with RoActemra. Certain types of vaccines should not be given while receiving RoActemra.

- If you have **cancer**, tell your doctor. Your doctor will have to decide if you can still be given RoActemra.

- If you have **cardiovascular risk factors** such as raised blood pressure and raised cholesterol levels, tell your doctor. These factors need to be monitored while receiving RoActemra.

- If you have moderate to severe **kidney function problems**, your doctor will monitor you.

- If you have **persistent headaches**.

Your doctor will perform a blood test before you receive RoActemra, to determine if you have a low white blood cell count, low platelet count or high liver enzymes.

Children and adolescents
RoActemra pre-filled pen is not recommended for use in children under 12 years of age. RoActemra must not be given to children with sJIA weighing less than 10 kg.

If a child has a history of ***macrophage activation syndrome*** (activation and uncontrolled proliferation of specific blood cells), tell your doctor. Your doctor will have to decide if they can still be given RoActemra.

Other medicines and RoActemra
Tell your doctor if you are taking any other medicines, or have recently taken any. RoActemra can affect the way some medicines work, and the dose of these may require adjustment. If you are using medicines containing any of the following active substances, **tell your doctor:**
- methylprednisolone, dexamethasone, used to reduce inflammation
- simvastatin or atorvastatin, used to reduce cholesterol levels
- calcium channel blockers (e.g. amlodipine), used to treat raised blood pressure
- theophylline, used to treat asthma
- warfarin or phenprocoumon, used as a blood thinning agents
- phenytoin, used to treat convulsions
- ciclosporin, used to suppress your immune system during organ transplants
- benzodiazepines (e.g. temazepam), used to relieve anxiety

Due to lack of clinical experience, RoActemra is not recommended for use with other biological medicines for the treatment of RA, sJIA, pJIA, or GCA.

Pregnancy, breast-feeding and fertility

RoActemra is not to be used in pregnancy unless clearly necessary. Talk to your doctor if you are pregnant, may be pregnant, or intend to become pregnant.

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

Stop breast-feeding if you are to be given RoActemra, and talk to your doctor. Leave a gap of at least 3 months after your last treatment before you start breast-feeding. It is not known whether RoActemra is passed into breast milk.

Driving and using machines
This medicine can cause dizziness. If you feel dizzy, do not drive or use machines.

RoActemra contains polysorbate
This medicine contains 0.18 mg of polysorbate 80 in each 162 mg/0.9 mL PFP which is equivalent to 0.2 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have or your child has any known allergies.

3. How to use RoActemra

Always use this medicine exactly as your doctor, pharmacist or nurse has told you. You should check with your doctor, pharmacist or nurse if you are not sure.

The treatment will be prescribed and started by healthcare professionals experienced in the diagnosis and treatment of RA, sJIA, pJIA or GCA.

The recommended dose
The dose with RA or GCA for all adults is 162 mg (the content of 1 pre-filled pen) given once a week.

Adolescents with sJIA (aged 12 years and over)
The usual dose of RoActemra depends on the patient's weight.
- If the patient weighs **less than 30 kg**: the dose is 162 mg (the content of 1 pre-filled pen) once every 2 weeks
- If the patient weighs **30 kg or more**: the dose is 162 mg (the content of 1 pre-filled pen) once every week

The pre-filled pen should not be used to treat children less than 12 years of age.

Adolescents with pJIA (aged 12 years and over)
The usual dose of RoActemra depends on the patient's weight.
- If the patient weighs **less than 30 kg**: the dose is 162 mg (the content of 1 pre-filled pen), **once every 3 weeks**
- If the patient weighs **30 kg or more**: the dose is 162 mg (the content of 1 pre-filled pen), **once every 2 weeks.**

The pre-filled pen should not be used to treat children less than 12 years of age.

RoActemra is given by injection under the skin (*subcutaneously*). At the start, your doctor or nurse may inject RoActemra. However, your doctor may decide that you may inject RoActemra yourself. In this case you will get training on how to inject RoActemra yourself. Parents and carers will get training on how to inject RoActemra for patients who cannot inject themselves.

Talk to your doctor if you have any questions about giving yourself or an adolescent patient you look after an injection. You will find detailed "Instructions for administration" at the end of this leaflet.

If you use more RoActemra than you should
Because RoActemra is given in one pre-filled pen, it is unlikely that you will receive too much. However, if you are worried, talk to your doctor, pharmacist or nurse.

If an adult with RA or GCA or an adolescent with sJIA misses or forgets a dose
It is very important to use RoActemra exactly as prescribed by your doctor. Keep track of your next dose.
- If you miss your weekly dose within 7 days, take your dose on the next scheduled day.
- If you miss your once every other week dose within 7 days, inject a dose as soon as you remember and take your next dose at your regular scheduled time.
- If you miss your weekly or once every other week dose by more than 7 days, or you are not sure when to inject RoActemra, call your doctor or pharmacist.

If an adolescent with pJIA misses or forgets a dose
It is very important to use RoActemra exactly as prescribed by the doctor. Keep track of the next dose.
- If a dose is missed within 7 days, inject a dose as soon as you remember and give the next dose at the regular scheduled time.
- If a dose is missed by more than 7 days, or you are not sure when to inject RoActemra, call the doctor or pharmacist.

If you stop using RoActemra
You should not stop using RoActemra without discussing with your doctor first.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, RoActemra can cause side effects, although not everybody gets them.
Side effects could occur 3 months or more after your last dose of RoActemra.

Possible serious side effects:
Tell your doctor **immediately** if you experience any of the following side effects:
These are common: they may affect up to 1 in every 10 people

Allergic reactions during or after injection:
- difficulty with breathing, chest tightness or light-headedness
- rash, itching, hives, swelling of the lips, tongue or face

Signs of serious infections:
- fever and chills
- mouth or skin blisters
- stomach ache

Signs and symptoms of liver toxicity:
These are rare: may affect up to 1 in every 1 000 people
- tiredness
- abdominal pain
- jaundice (yellow discolouration of skin or eyes)

List of other possible side effects
If you notice any of these, tell your doctor **as soon as possible**:

Very common side effects:
These may affect 1 in 10 people or more
- upper respiratory tract infections with typical symptoms such as cough, blocked nose, runny nose, sore throat and headache
- high blood fat (*cholesterol*) levels
- injection site reactions

Common side effects:
These may affect up to 1 in 10 people
- lung infection (pneumonia)
- shingles (herpes zoster)
- cold sores (oral herpes simplex), blisters
- skin infection (cellulitis) sometimes with fever and chills
- rash and itching, hives

- allergic (hypersensitivity) reactions
- eye infection (conjunctivitis)
- headache, dizziness, high blood pressure
- mouth ulceration, stomach pain
- fluid retention (oedema) in the lower legs, weight increase
- cough, shortness of breath
- low white blood cell counts shown by blood tests (neutropenia, leucopenia)
- abnormal liver function tests (increased transaminases)
- increased bilirubin shown by blood tests
- low fibrinogen levels in the blood (a protein involved in blood clotting)

Uncommon side effects:
These may affect up to 1 in every 100 people
- diverticulitis (fever, nausea, diarrhoea, constipation, stomach pain)
- red swollen areas in the mouth
- high blood fat (triglycerides)
- stomach ulcer
- kidney stones
- underactive thyroid

Rare side effects:
These may affect up to 1 in every 1 000 people
- Stevens-Johnson Syndrome (skin rash, which may lead to severe blistering and peeling of the skin)
- fatal allergic reactions (anaphylaxis)
- inflammation of the liver (hepatitis), jaundice

Very rare side effects:
These may affect up to 1 in every 10 000 people
- low counts for white blood cells, red blood cells and platelets in blood tests
- liver failure

Side effects in children and adolescents with sJIA or pJIA
Side effects in children and adolescents with sJIA or pJIA are generally similar to those in adults. Some side effects are seen more often in children and adolescents: inflamed nose and throat, headache, feeling sick (nausea) and lower white blood cell counts.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store RoActemra

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pre-filled pen label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze. Once removed from the refrigerator, the pre-filled pen can be stored up to 2 weeks at or below 30 °C

Keep the pre-filled pens in the outer carton in order to protect from light and moisture.

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

The pen should not be shaken. After removing the cap the injection must be started within 3 minutes to prevent the medicine from drying out and blocking the needle. If the pre-filled pen is not used within 3 minutes of cap removal, you must dispose of it in a puncture resistant container and use a new pre-filled pen.

If following pressing the activation button the purple indicator does not move, you must dispose of the pre-filled pen in a puncture resistant container. **Do not** try to re-use the pre-filled pen. Do not repeat the injection with another pre-filled pen. Call your healthcare provider for help.

6. Contents of the pack and other information

What RoActemra contains

- The active substance is tocilizumab.

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

- The other ingredients are L-Histidine, L-Histidine monohydrochloride monohydrate, L-Arginine/L-Arginine hydrochloride, L-Methionine, Polysorbate 80 and Water for injections (see section 2 ‘RoActemra contains polysorbates’).

What RoActemra looks like and contents of the pack

RoActemra is a solution for injection. The solution is colourless to slightly yellowish.
RoActemra is supplied as a 0.9 mL pre-filled pen containing 162 mg tocilizumab solution for injection. Each pack contains 4 pre-filled pens with multipacks containing 12 (3 packs of 4) pre-filled pens. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

Manufacturer

Roche Pharma AG
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Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Luxembourg/Luxemburg
(Voir/siehe Belgique/Belgien)

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România
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Slovenija
Roche farmacevtska družba d.o.o.
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Slovenská republika
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Suomi/Finland
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Sverige
Roche AB
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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu.

What you need to know to use your RoActemra pre-filled pen (ACTPen) safely.

Read and follow the Instructions for Use that come with your RoActemra pre-filled pen before you start using it and each time you get a prescription refill. Before you use the RoActemra pre-filled pen for the first time, make sure your healthcare provider shows you the right way to use it.

Important: Keep your unused pre-filled pens in the original carton and keep in the refrigerator at 2 °C to 8 °C. **Do not** freeze.

Once removed from the refrigerator, the pre-filled pen can be stored for a total time of up to 2 weeks at or below 30 °C, but not exceeding the original expiry date (EXP). Mark the relevant date on the carton. Always keep the pre-filled pens in the outer carton in order to protect from light and moisture.

- Do not remove the pre-filled pen cap until you are ready to inject RoActemra.
- Do not try to take apart the pre-filled pen at any time.
- Do not reuse the same pre-filled pen.
- Do not use the pre-filled pen through clothing.
- Do not leave the pre-filled pen unattended.
- Keep out of the reach of children.

Parts of your RoActemra pre-filled pen **(See Figure A).**

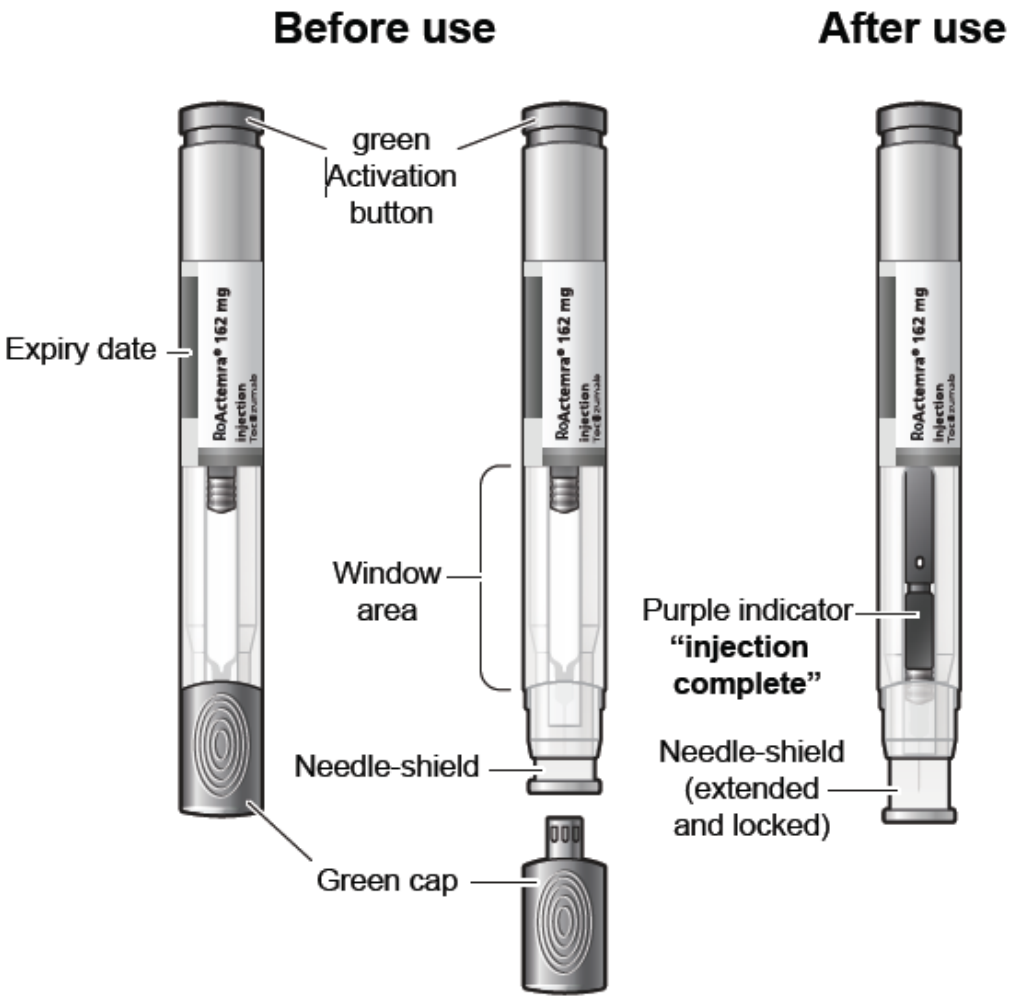

Figure A

Supplies needed for an injection using your RoActemra pre-filled pen (See Figure B):

- 1 RoActemra pre-filled pen
- 1 Alcohol pad
- 1 Sterile cotton ball or gauze
- 1 Puncture-resistant container or sharps container for safe disposal of pre-filled pen cap and used pre-filled pen (see **Step 4 "Dispose of the pre-filled pen")**

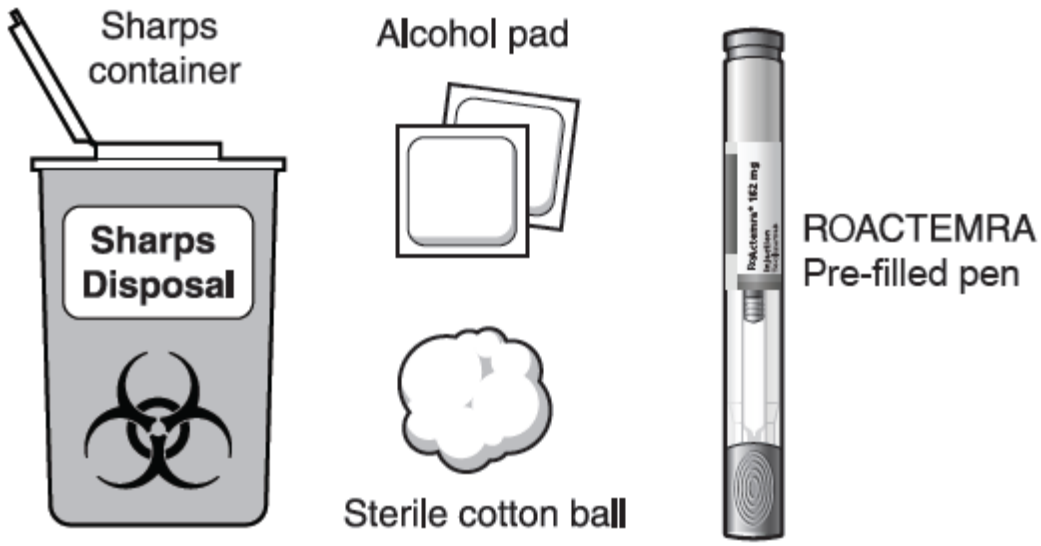

Figure B

Step 1. Preparing for a RoActemra Injection
Find a comfortable space with a clean, flat, working surface.

- Take the box containing the pre-filled pen out of the refrigerator.
- If you are opening the box for the first time, check to make sure that it is properly sealed. **Do not** use the pre-filled pen if the box looks like it has already been opened.
- Check that the pre-filled pen box is not damaged. **Do not** use RoActemra pre-filled pen if the box looks damaged.
- **Check the expiry date on the pre-filled pen box**. **Do not** use the pre-filled pen if the expiry date has passed because it may not be safe to use.
- Open the box, and remove 1 single-use RoActemra pre-filled pen from the box.
- Return any remaining pre-filled pens in the box to the refrigerator.
- **Check the expiry date on the RoActemra pre-filled pen (See Figure A). Do not** use it if the expiry date has passed because it may not be safe to use. If the expiry date has passed, safely dispose of the pre-filled pen in a sharps container and get a new one.
- **Check the pre-filled pen to make sure it is not damaged.** Do not use the pre-filled pen if it appears to be damaged or if you have accidentally dropped the pre-filled pen.
- Place the pre-filled pen on a clean, flat surface and let the pre-filled pen warm up for 45 minutes to allow it to reach room temperature. If the pre-filled pen does not reach room temperature, this could cause your injection to feel uncomfortable and it could take longer to inject.

- **Do not** speed up the warming process in any way, such as using the microwave or placing the pre-filled pen in warm water.
- **Do not** leave the pre-filled pen to warm up in direct sunlight.

Do not remove the green cap while allowing your RoActemra pre-filled pen to reach room temperature.

- Hold your RoActemra pre-filled pen with the green cap pointing down **(See Figure C).**

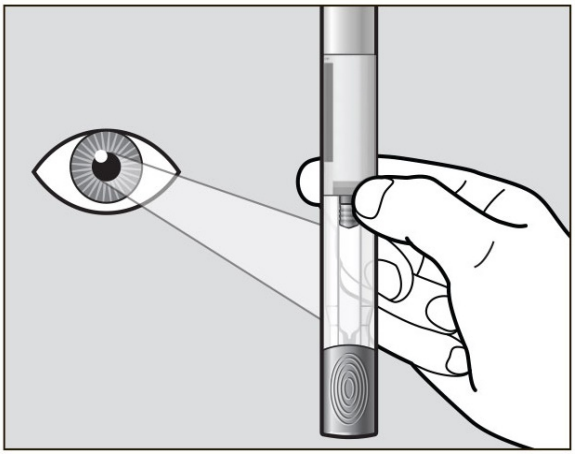

Figure C

- Look in the clear Window area. Check the liquid in the RoActemra pre-filled pen **(See Figure C)**. It should be clear and colourless to pale yellow. **Do not** inject RoActemra if the liquid is cloudy, discoloured, or has lumps or particles in it because it may not be safe to use. Safely dispose of the pre-filled pen in a sharps container and get a new one.
- Wash your hands well with soap and water.

Step 2. Choose and Prepare an Injection Site

Choose an Injection Site

- The front of your thigh or your abdomen except for the 2-inch (5cm) area around your navel are the recommended injection sites **(See Figure D).**
- The outer area of the upper arms may also be used only if the injection is being given by a caregiver. Do not attempt to use the upper arm area by yourself **(See Figure D).**

Rotate Injection Site

- Choose a different injection site for each new injection at least 1-inch (2.5cm) from the last area you injected.
- Do not inject into moles, scars, bruises, or areas where the skin is tender, red, hard or not intact.

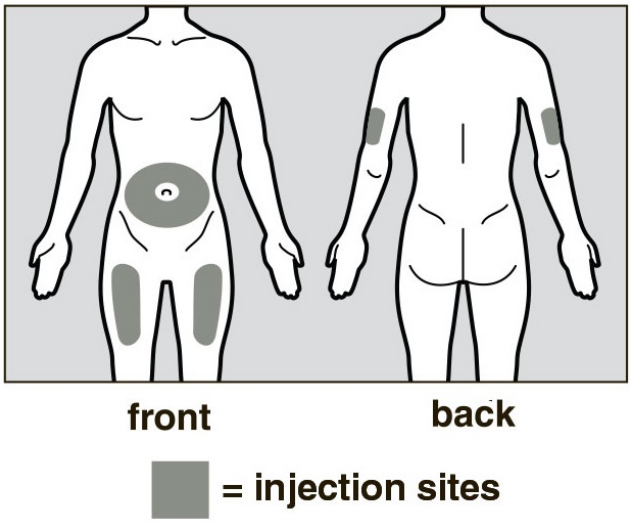

Figure D

Prepare the Injection Site

- Wipe the injection site with an alcohol pad in a circular motion and let it air dry to reduce the chance of getting an infection. **Do not** touch the injection site again before giving the injection.
- **Do not** fan or blow on the clean area.

Step 3. Inject RoActemra

- Hold the RoActemra pre-filled pen firmly with one hand. Twist and pull off the green cap with the other hand **(See Figure E).** The green cap contains a loose fitting metal tube.
- If you cannot remove the green cap you should ask a caregiver for help or contact your healthcare provider.

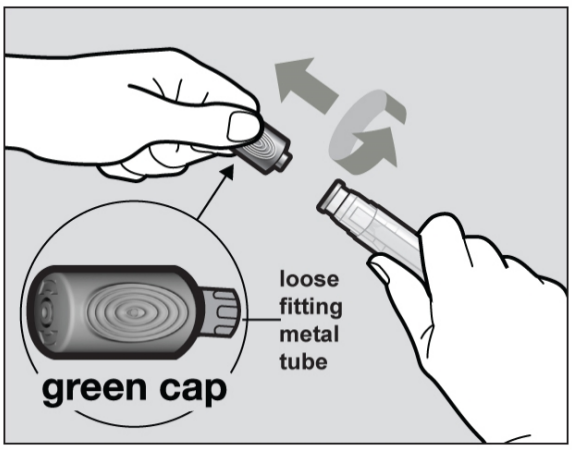

Figure E

Important: Do not touch the needle shield which is located at the tip of the pre-filled pen below the window area (see Figure A), to avoid accidental needle stick injury.

- Throw away the green cap in a sharps container.
- After you remove the green cap, the pre-filled pen is ready for use. If the pre-filled pen is not used within 3 minutes of the cap removal, the pre-filled pen should be disposed of in the sharps container and a new pre-filled pen should be used.
- Never reattach the green cap after removal.
- Hold the pre-filled pen comfortably in 1 hand by the upper part, so that you can see the Window area of the pre-filled pen **(See Figure F).**

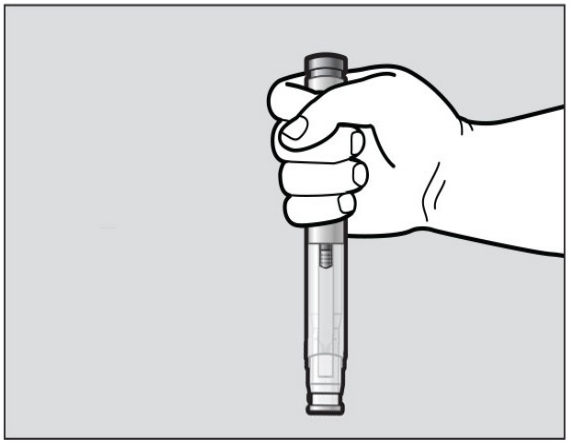

Figure F

- Use your other hand to gently pinch the area of skin you cleaned, to prepare a firm injection site **(See Figure G).** The pre-filled pen requires a firm injection site to properly activate.
- Pinching the skin is important to make sure that you inject under the skin (into fatty tissue) but not any deeper (into muscle). Injection into muscle could cause the injection to feel uncomfortable.

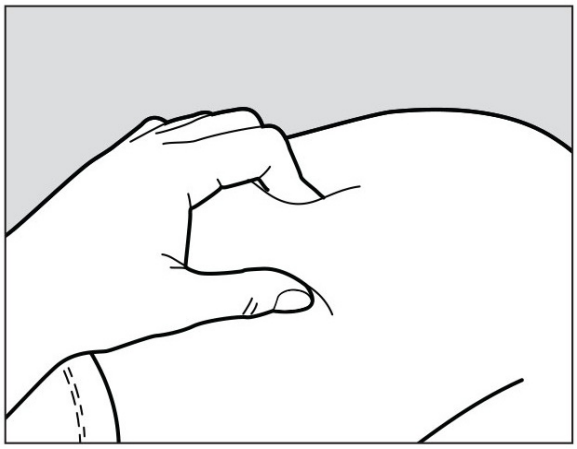

Figure G

- **Do not** press the green activation button yet.
- Place the needle-shield of the pre-filled pen against your pinched skin at a 90° angle **(See Figure H).**
- It is important to use the correct angle to make sure the medicine is delivered under the skin (into fatty tissue), or the injection could be painful and the medicine may not work.

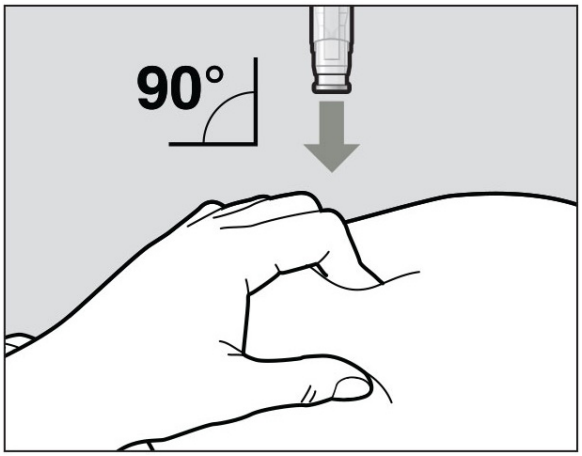

Figure H

- To use the pre-filled pen, you first have to unlock the green Activation button.
- To unlock it, press the pre-filled pen firmly against your pinched skin until the needle-shield is completely pushed in **(See Figure I)**.

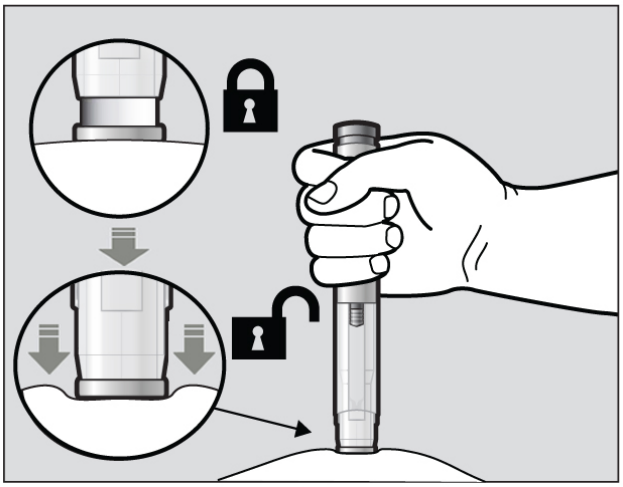

Figure I

- Continue to keep the needle-shield pushed in.
- If you don't keep the needle-shield completely pushed against the skin, the green Activation button will not work.
- Continue to pinch the skin while you keep the pre-filled pen in place.
- Press the green Activation button to start the injection. A "click" sound indicates the start of the injection. Keep the green button pressed in and continue holding the pre-filled pen pressed firmly against your skin **(See Figure J).** If you cannot start the injection you should ask for help from a caregiver or contact your healthcare provider.

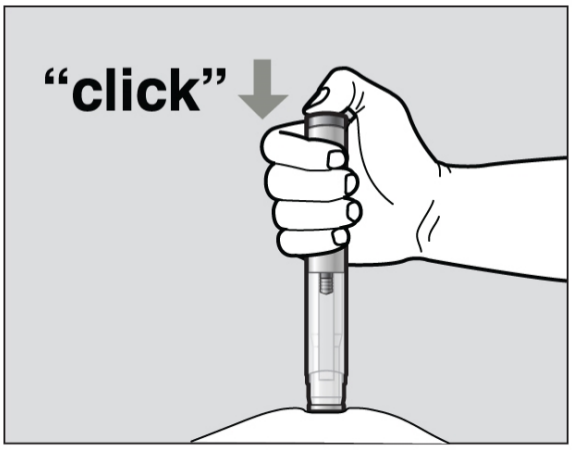

Figure J

- The purple indicator will move along the Window area during the injection **(See Figure K).**
- Watch the purple indicator until it stops moving to be sure the full dose of medication is injected.

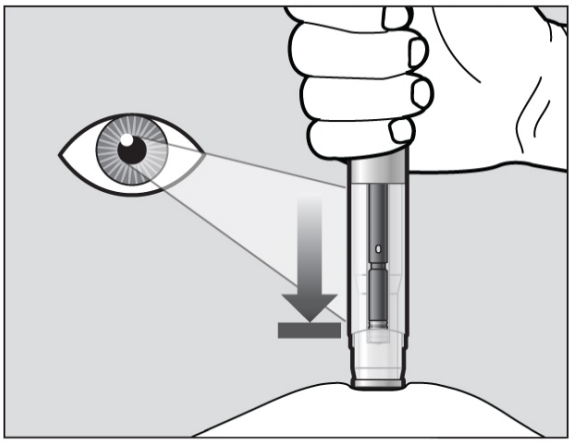

Figure K

- The injection may take up to **10 seconds**.
- You may hear a second “click” during the injection but you should continue to hold the pre-filled pen firmly against your skin until the purple indicator stops moving.
- When the purple indicator has stopped moving, release the green button. Lift the pre-filled pen straight off of the injection site at a 90° angle to remove the needle from the skin. The needle-shield will then move out and lock into place covering the needle **(See Figure L)**.

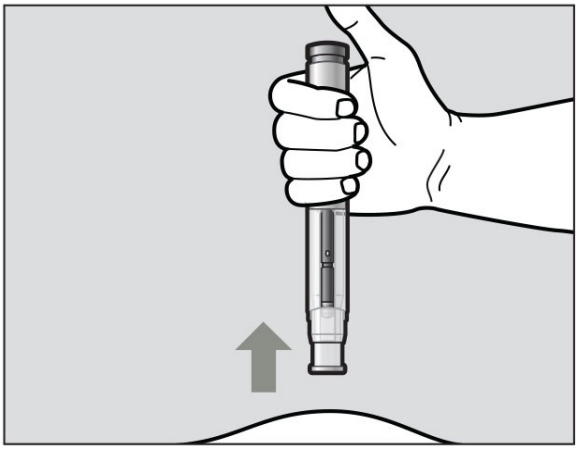

Figure L

- Check the Window area to see that it is filled with the purple indicator **(See Figure L).**
- If the Window area is not filled by the purple indicator then:
    - The needle-shield may not have locked. **Do not** touch the needle-shield of the pre-filled pen, because you may stick yourself with the needle. If the needle is not covered, carefully place the pre-filled pen into the sharps container to avoid any injury with the needle.
    - You may not have received your full dose of RoACTEMRA. **Do not** try to re-use the pre-filled pen. Do not repeat the injection with another pre-filled pen. Call your healthcare provider for help.

After the Injection

- There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.
- **Do not** rub the injection site.
- If needed, you may cover the injection site with a small bandage.

Step 4. Dispose of the pre-filled pen

- The RoActemra pre-filled pen should not be reused.
- Put the used pre-filled pen into your sharps container (see **“How do I dispose of used pre-filled pens?”)**

- **Do not** put the cap back on the pre-filled pen.

• If your injection is given by another person, this person must also be careful when removing the pre-filled pen and disposing of it to prevent accidental needle stick injury and passing infection.

How do I dispose of used pre-filled pens?

• Put your used RoActemra pre-filled pen and green cap in a sharps disposal container right away after use **(See Figure M).**

• Do not throw away (dispose of) the pre-filled pen and the green cap in your household trash and do not recycle them.

Figure M

• Dispose of the full container as instructed by your healthcare provider or pharmacist.
• Always keep the puncture-resistant container out of the sight and reach of children.

Keep the RoActemra pre-filled pen and disposal container out of the reach of children.

Record your Injection

• Write the date, time, and specific part of your body where you injected yourself. It may also be helpful to write any questions or concerns about the injection so you can ask your healthcare provider.

If you have any questions or concerns about your RoActemra pre-filled pen, talk to your healthcare provider familiar with RoActemra.