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 against the human interleukin-6 (IL - 6) receptor produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipients with known effects
Each 80 mg vial contains 0.10 mmol (2.21 mg) sodium.
Each 200 mg vial contains 0.20 mmol (4.43 mg) sodium.
Each 400 mg vial contains 0.39 mmol (8.85 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to opalescent, colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX .
- 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 diseasemodifying 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.

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

RoActemra is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX .

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

RoActemra is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (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, COV ID-19, sJIA, pJIA or CRS.

All patients treated with RoActemra should be given the Patient Alert 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 studies (see section 5.1).

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

· Liver enzyme abnormalities

Laboratory Value	Action

> 1 to 3 x Upper L imit of Normal (UL N)	Modify the dose of the concomitant MTX if appropriate. For persistent increases in this range, reduce RoActemra dose to 4 mg/kg or interrupt RoActemra until alanine aminotransferase (AL T) or aspartate aminotransferase (AST) have normalized. Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate.
> 3 to 5 x UL N (confirmed by repeat testing, see section 4.4).	Interrupt RoActemra dosing until < 3 x UL N and follow recommendations above for > 1 to 3 x UL N. For persistent increases > 3 x UL N, discontinue RoActemra.
> 5 x UL N	Discontinue RoActemra.

· L ow absolute neutrophil count (ANC)

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

Laboratory Value (Cells x 10^9/ l)	Action
ANC > 1	Maintain dose.
ANC 0.5 to 1	Interrupt RoActemra dosing. When ANC increases > 1 x 10^9/ l resume RoActemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate.
ANC < 0.5	Discontinue RoActemra.

· L ow platelet count

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

COVID-19 Patients

The recommended posology for treatment of COV ID-19 is a single 60-minute intravenous infusion of 8 mg/kg 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 RoActemra 8 mg/kg may be administered. The interval between the two infusions should 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 RoActemra is not recommended in patients with COV ID-19 who have any of the following laboratory abnormalities:

Laboratory test type	**Laboratory value**	**Action**
Liver enzyme	≥10x UL N	Administration of RoActemra is not recommended
Absolute neutrophil count	< 1 x 10^9 /L	
Platelet count	< 50 x 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. RoActemra 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 RoActemra may be administered. The interval between consecutive doses should 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 AL T or AST due to the underlying malignancy, preceding lymphodepleting chemotherapy or the CRS.

Special populations

Paediatric patients
sJIA Patients

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

The safety and efficacy of intravenous RoActemra in children below 2 years of age has not been established.

Dose interruptions of tocilizumab for the following laboratory abnormalities are recommended in sJIA patients in the tables below. If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical

situation has been evaluated. As there are many co-morbid conditions that may affect laboratory values in sJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.

· Liver enzyme abnormalities

Laboratory Value	Action
> 1 to 3 x UL N	Modify the dose of the concomitant MTX if appropriate. For persistent increases in this range, interrupt RoActemra until AL T/AST have normalized.
> 3 x UL N to 5x UL N	Modify the dose of the concomitant MTX if appropriate. Interrupt RoActemra dosing until < 3x UL N and follow recommendations above for >1 to 3x UL N.
> 5x UL N	Discontinue RoActemra. The decision to discontinue RoActemra in sJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

· L ow absolute neutrophil count (ANC)

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

· L ow platelet count

Laboratory Value (cells x 10^3/$_m$l)	Action
50 to 100	Modify the dose of the concomitant MTX if appropriate. Interrupt RoActemra dosing. When platelet count is > 100 x 10^3/ml resume RoActemra.

< 50	Discontinue RoActemra. The decision to discontinue RoActemra in sJIA for a laboratory abnormality should 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 RoActemra. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe.

pJIA Patients

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

The safety and efficacy of intravenous RoActemra in children below 2 years of age has not been established.

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

· Liver enzyme abnormalities

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

> 5x UL N	Discontinue RoActemra. The decision to discontinue RoActemra in pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

· L ow absolute neutrophil count (ANC)

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

· Low platelet count

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

Reduction of tocilizumab dose due to laboratory abnormalities has not been studied in pJIA patients.
Available data suggest that clinical improvement is observed within 12 weeks of initiation of treatment with RoActemra. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe.

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. RoActemra has not been studied in patients with moderate to severe renal

impairment (see section 5.2). Renal function should be monitored closely in these patients.

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

Method of administration

After dilution, RoActemra for RA, sJIA, pJIA, CRS, and COV ID-19 patients should be administered as an intravenous infusion over 1 hour.

RA, sJIA, pJIA, CRS and COV ID-19 Patients ≥ 30 kg
RoActemra should be diluted to a final volume of 100 mL with sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection using aseptic technique.

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

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

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

If signs and symptoms of an infusion related reaction occur, slow or stop the infusion and administer appropriate medication/ supportive care immediately, see section 4.4.

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 COV ID-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 RoActemra (see section 4.8,

undesirable effects). RoActemra treatment must not be initiated in patients with active infections (see section 4.3). Administration of RoActemra should be interrupted if a patient develops a serious infection until the infection is controlled (see section 4.8). Healthcare professionals should exercise caution when considering the use of RoActemra 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 should be considered when evaluating a patient for a potential infection. Patients (which includes younger children with sJIA or pJIA who may be less able to communicate their symptoms) and parents/guardians of sJIA or pJIA patients should be instructed to contact their healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

Tuberculosis
As recommended for other biological treatments, RA, sJIA and pJIA patients should be screened for latent tuberculosis (TB) infection prior to starting RoActemra therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating RoActemra. 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 RoActemra.

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

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

Hypersensitivity reactions

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

Active hepatic disease and hepatic impairment
Treatment with RoActemra, 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 RoActemra treatment (see section 4.8). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with RoActemra. 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 RoActemra (see section 4.8). Serious hepatic injury occurred between 2 weeks to more than 5 years after initiation of RoActemra. Cases of liver failure resulting in liver transplantation have been reported. Patients should be advised to immediately seek medical help if they experience signs and symptoms of hepatic injury.

Caution should be exercised when considering initiation of RoActemra treatment in patients with elevated AL T or AST > 1.5 x UL N. In RA, pJIA and sJIA patients with baseline AL T or AST > 5 x UL N, treatment is not recommended.

In RA, pJIA and sJIA patients, AL T/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 RoActemra discontinuation, based on transaminases levels see section 4.2. For AL T or AST elevations > 3–5 x UL N, confirmed by repeat testing, RoActemra 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 RoActemra, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/L . Caution should be exercised when considering initiation of RoActemra treatment in patients with a low platelet count (i.e. platelet count below 100 x 10^3/ µL). In RA, sJIA and pJIA patients who develop an ANC < 0.5 x 10^9/ l or a platelet count < 50 x 10^3/µL , continued treatment is not recommended.

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

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

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

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

In sJIA, pJIA and RA patients, assessment of lipid parameters should be performed 4 to 8 weeks following initiation of RoActemra 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 RoActemra is currently unknown.

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

Vaccinations
Live and live attenuated vaccines should not be given concurrently with RoActemra as clinical safety has not been established. In a randomized open-label study, adult RA patients treated with RoActemra and MTX were able to mount an effective response to both the 23-valent pneumococcal polysaccharide and tetanus toxoid vaccines which was comparable to the response seen in patients on MTX only. It is recommended that all patients, particularly sJIA and pJIA patients, be brought up to date with all

immunisations in agreement with current immunisation guidelines prior to initiating RoActemra therapy. The interval between live vaccinations and initiation of RoActemra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

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

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

Sodium
This medicinal product contains 1.17 mmol (or 26.55 mg) sodium per maximum dose of 1200 mg. To be taken into consideration by patients on a controlled sodium diet. Doses below 1025 mg of this medicinal product contain less than 1 mmol sodium (23 mg), i.e. essentially 'sodium free'.

COV ID-19 Patients

- The efficacy of RoActemra has not been established in the treatment of COV ID-19 patients who do not have elevated CRP levels, see section 5.1
- RoActemra should not be administered to COV ID-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 COV ID-19 patients, RoActemra should not be administered if they have any other concurrent severe active infection. Healthcare professionals should exercise caution when considering the use of RoActemra 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 hospitalized with COV ID-19 may have elevated AL T or AST levels. Multi-organ failure with involvement of the liver is recognized as a complication of severe COV ID-19. The decision to administer tocilizumab should balance the potential benefit of treating COV ID-19 against the potential risks of acute treatment with tocilizumab. In COV ID-19 patients with elevated AL T or AST above 10 x UL N, administration of RoActemra treatment is not recommended. In COV ID-19 patients, AL T /AST should be monitored according to current standard clinical practices.

Haematological abnormalities
In COV ID-19 patients who develop an ANC < 1 x 10^9 /L or a platelet count < 50 x 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 , non-steroidal antiinflammatory drugs (NSAIDs) or corticosteroids on tocilizumab clearance.

The expression of hepatic CY P450 enzymes is suppressed by cytokines, such as IL -6, that stimulate chronic inflammation. Thus, CY P450 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
CY P1A2, CY P2C9, CY P2C19 and CY P3A4 enzyme expression. Tocilizumab normalises expression of these enzymes.

In a study in RA patients, levels of simvastatin (CY P3A4) 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 CY P450 3A4, 1A2 or 2C9 (e.g. . methylprednisolone, dexamethasone, (with the possibility for oral glucocorticoid withdrawal syndrome), atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses may need to be increased to maintain therapeutic effect. Given its long elimination half-life ($t_{1/2}$), the effect of tocilizumab on CY P450 enzyme activity may persist for several weeks after stopping therapy.

4.6 fertility, pregnancy and lactation

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

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

RoActemra should not be used during pregnancy unless clearly necessary.

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported ADRs (occurring in ≥5% of patients treated with tocilizumab monotherapy or in combination with DMARDs for RA, sJIA, pJIA and CRS) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased AL T.

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

The most commonly reported ADRs (occurring in ≥ 5% of patients treated with tocilizumab for COV ID-19) were hepatic transaminases increased, constipation, and urinary tract infection.

ADRs from clinical trials and/or post marketing experience with RoActemra 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. The corresponding frequency category for each ADR is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (>1/10,000 to

<1/1,000) or very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

RA Patients

The safety profile 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.

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

MedDR A System Organ C lass	` requency categories with preferred terms			
	Very C ommon	C ommon	Uncommon	R are
Infections and infestations	Upper respiratory tract infections	Cellulitis, Pneumonia, Oral herpes simplex, Herpes zoster	Diverticulitis	
Blood and lymphatic system disorders		L eukopenia, Neutropenia, Hypofibrinogenae mia		
Immune system disorders				Anaphylaxis (fatal)1, 2 ,3
Endocrine disorders			Hypothyroidism	
MedDR A System Organ C lass	F requency categories with preferred terms			
	Very C ommon	C ommon	Uncommon	R are
Metabolism and nutrition disorders	Hypercholesterola emia*		Hypertriglyceridae mia	
Nervous system disorders		Headache, Dizziness		

Eye disorders		Conjunctivitis		
V ascular 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, V ery rare: Hepatic failure
Skin and subcutaneous tissue disorders		Rash, Pruritus, Urticaria		Stevens-JohnsonSyndrome[3]
Renal and urniary disorders			Nephrolithiasis	
General disorders and administration site conditions		Peripheral oedema, Hypersensitivity reactions		
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.

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 RoActemra was 108 events per 100 patient years exposure.

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

infections was 3.6 events per 100 patient years of exposure in the tocilizumab group and 1.5 events per 100 patient years of exposure in the MTX group.

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

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

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

Infusion 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 with tocilizumab during the controlled and open label clinical studies. These reactions were generally observed during the second to fifth infusions of tocilizumab (see section 4.4). Fatal anaphylaxis has been reported after marketing authorisation during treatment with tocilizumab (see section 4.4).

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

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

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

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

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

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

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

The addition of potentially hepatotoxic drugs (e.g. MTX) to tocilizumab monotherapy resulted in increased frequency of these elevations. Elevations of AL T/AST > 5 x UL N 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 x UL N and 0.4% had an elevation of > 2 x UL N.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevation in AL T/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, L DL cholesterol, and/or HDL cholesterol have been reported commonly. With routine laboratory monitoring it was seen that approximately 24% of patients receiving RoActemra in clinical trials experienced sustained elevations in total cholesterol ≥ 6.2 mmol/ l, with 15% experiencing a sustained increase in L DL to ≥ 4.1 mmol/ l. Elevations in lipid parameters responded to treatment with lipid-lowering agents.

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

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

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

Patients with COV ID-19
The safety evaluation of RoActemra in COV ID-19 was based on 3 randomized, double-blind, placebo controlled trials (studies ML 42528, WA42380, and WA42511). A total of 974 patients were exposed to RoActemra in these studies. Collection of safety data from RECOV ERY was limited and is not presented here.

The following adverse reactions, listed by MedDRA system organ class in Table 2, have been adjudicated from events which occurred in at least 3% of RoActemra treated patients and more commonly than that in patients on placebo in the pooled safety-evaluable population from clinical studies ML 42528, WA42380, and WA42511.
Table 2: List of Adverse Reactions[1] Identified From the Pooled Safety-Evaluable Population From RoActemra Clinical Studies in COVID-19 patients[2]

MedDR A System Organ C lass	Very C ommon	C ommon
Infections and infestations		Urinary tract infection
Metabolism and nutrition disorders		Hypokalaemia
Psychiatric disorders		Anxiety, Insomnia
V ascular 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 ML 42528

Description of selected adverse drug reactions

Infections
In the pooled safety-evaluable population from studies ML 42528, WA42380, and WA42511, the rates of infection/serious infection events were balanced between COV ID-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 IV 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 COV ID -19 who received one or two doses of RoActemra-IV compared with those who received placebo in the randomized, double-blind, placebo controlled trials with few exceptions. Decreases in platelets and neutrophils and elevations of AL T and AST were more frequent among patients receiving RoActemraIV versus placebo (see section 4.2 and 4.4).

sJIA and pJIA Patients

The safety profile of tocilizumab in the paediatric population is summarized in the sections on pJIA and sJIA below. In general, the ADRs in pJIA and sJIA patients were similar in type to those seen in RA patients, see section 4.8.

ADRs in the pJIA and sJIA patients treated with tocilizumab are listed in the Table3 and presented by MedDRA system organ class. The corresponding frequency category for each ADR is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10) or uncommon (≥ 1/1,000 to <1/100).
Table 3: List of ADRs occurring in clinical trial patients with sJIA or pJIA receiving tocilizumab as monotherapy or in combination with MTX.

MedDR A 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	
	Diarrhea		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, epigastricdiscomfort, arthralgia and headache

pJIA Patients

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

Infections

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

Infusion 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 drug reactions observed during or within 24 hours of an infusion were similar in nature to those seen in RA and sJIA patients, see section 4.8.

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

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

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

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

Hepatic transaminase elevations
During routine laboratory monitoring in the tocilizumab all exposure population, elevation in AL T or AST ≥ 3xUL N occurred in 3.7% and <1% of patients, respectively.

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

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

In general, the ADRs in sJIA patients were similar in type to those seen in RA patients, see section 4.8. The frequency of ADRs in sJIA patients can be found in Table 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 diarrhea. Events of cholesterol increased were less frequently reported in the sJIA population than in the adult RA population.

Infections
In the 12 week controlled phase, the rate of all infections in the intravenous RoActemra 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 RoActemra 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, diarrhea, epigastric discomfort, arthralgia and headache. One of these events, urticaria, was considered serious.

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

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

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

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

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

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

Hepatic transaminase elevations
During routine laboratory monitoring in the 12 week controlled phase, elevation in AL T or
AST ≥ 3 x UL N 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 AL T or AST ≥ 3 x UL N 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 L DL -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 postbaseline elevation of their L DL -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 Tcell-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 authorization 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 RoActemra. One case of accidental overdose was reported in which a patient with multiple myeloma received a single dose of 40 mg/kg. No adverse reactions were observed.

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

Paediatric population

No case of an overdose in the paediatric population has been observed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors; ATC code: L 04AC07.

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

Pharmacodynamic effects
In clinical studies with 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 tocilizumab-treated patients, decreases in the levels of CRP to within normal ranges were seen as early as week 2, with decreases maintained while on treatment.

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

In COV ID-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 studies. Studies I-V enrolled patients ³ 18 years of age with active RA diagnosed according to the American College of Rheumatology (ACR) criteria and who had at least eight tender and six swollen joints at baseline.

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

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

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

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

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

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

Clinical response
In all studies, patients treated with tocilizumab 8 mg/kg had statistically significant higher ACR 20, 50, 70 response rates at 6 months compared to control (Table 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 studies I-V .

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

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

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

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

	Study I AMBIT ION	Study II L IT H E	Study III OPT ION	Study IV T OWAR D	Study V R ADIAT E

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

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

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

Radiographic response
In Study II, in patients with an inadequate response to MTX , inhibition of structural joint damage was assessed radiographically and expressed as change in modified Sharp score and its components, the erosion score and joint space narrowing score. Inhibition of joint structural damage was shown with significantly less radiographic progression in patients receiving tocilizumab compared to control (Table 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 + MT X (+ T C Z from week 24) N = 393	T C Z 8 mg/kg + MT X N = 398
Total Sharp-Genant score	1.13	0.29*
Erosion score	0.71	0.17*
JSN score	0.42	0.12**

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

Following 1 year of treatment with tocilizumab plus MTX , 85% of patients (n=348) had no progression of structural joint damage, as defined by a change in the Total Sharp Score of zero or less, compared with 67% of placebo plus MTX -treated patients (n=290) (p £ 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 RoActemra 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 V I (WA19924), a 24 week double-blinded study that compared tocilizumab monotherapy with adalimumab monotherapy, evaluated 326 patients with RA who were intolerant of MTX or where continued treatment

with MTX was considered inappropriate (including MTX inadequate responders). Patients in the tocilizumab arm received an intravenous (IV) infusion of tocilizumab (8 mg/kg) every 4 weeks (q4w) and a subcutaneous (SC) placebo injection every 2 weeks (q2w). Patients in the adalimumab arm received an adalimumab SC injection (40 mg) q2w plus an IV placebo infusion q4w. A statistically significant superior treatment effect was seen in favour of tocilizumab over adalimumab in control of disease activity from baseline to week 24 for the primary endpoint of change in DAS28 and for all secondary endpoints (Table 6).

Table 6: Efficacy Results for Study VI (WA19924)

	ADA + Placebo (IV) N = 162	T C Z + Placebo (SC) N = 163	p-value[a]
Primary E ndpoint - Mean C hange 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 E ndpoints - Percentage of R esponders at Week 24 [b]			
DAS28 < 2.6, n (%)	17 (10.5)	65 (39.9)	<0.0001
DAS28 ≤ 3.2, n (%)	32 (19.8)	84 (51.5)	<0.0001
ACR20 response, n (%)	80 (49.4)	106 (65.0)	0.0038
ACR50 response, n (%)	45 (27.8)	77 (47.2)	0.0002
ACR70 response, n (%)	29 (17.9)	53 (32.5)	0.0023

[a]p value is adjusted for region and duration of RA for all endpoints and additionally baseline value for all continuous endpoints.

[b] Non-responder Imputation used for missing data. Multiplicity controlled using Bonferroni-Holm Procedure

The overall clinical adverse event profile was similar between tocilizumab and adalimumab. The proportion of patients with serious adverse events was balanced between the treatment groups (tocilizumab 11.7% vs. adalimumab 9.9%). The types of adverse drug reactions in the tocilizumab arm were consistent with the known safety profile of tocilizumab and adverse drug reactions were reported at a similar frequency compared with Table 1. A higher incidence of infections and infestations was reported in the tocilizumab arm (48% vs. 42%), with no difference in the incidence of serious infections (3.1%). Both study treatments induced the same pattern of changes in laboratory safety parameters (decreases in neutrophil and platelet counts, increases in AL T, 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 AL T increases of CTC grade 2 or higher. The mean L DL increase from baseline was 0.64 mmol/L (25 mg/dL) for patients in the tocilizumab arm and 0.19 mmol/L (7 mg/dL) for patients in the

adalimumab arm. The safety observed in the tocilizumab arm was consistent with the known safety profile of tocilizumab and no new or unexpected adverse drug reactions were observed (see Table 1).

MTX naïve, Early RA

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

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

		T C Z 8 mg/kg + MT X N=290	T C Z 8 mg/kg + placebo N=292	T C Z 4 mg/kg + MT X N=288	Placebo + MT X N=287
Primary E ndpoint					
DAS28 Remission					
Week 24	n (%)	130 (44.8)***	113 (38.7)***	92 (31.9)	43 (15.0)
K ey Secondary E ndpoints					
DAS 28 remission					
Week 52	n (%)	142 (49.0)***	115 (39.4)	98 (34.0)	56 (19.5)
ACR					
Week 24	ACR20, n (%)	216 (74.5)*	205 (70.2)	212 (73.6)	187 (65.2)
	ACR50, n (%)	165 (56.9)**	139 (47.6)	138 (47.9)	124 (43.2)
	ACR70, n (%)	112 (38.6)**	88 (30.1)	100 (34.7)	73 (25.4)

Week 52	ACR20, n (%)	195 (67.2)*	184 (63.0)	181 (62.8)	164 (57.1)
	ACR50, n (%)	162 (55.9)**	144 (49.3)	151 (52.4)	117 (40.8)
	ACR70, n (%)	125 (43.1)**	105 (36.0)	107 (37.2)	83 (28.9)
HAQ-DI (adjusted mean change from baseline)					
Week 52		-0.81*	-0.67	-0.75	-0.64
R adiographic E ndpoints (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)
E xploratory E ndpoints					
	Week 24: ACR/EUL AR Boolean Remission, n (%)	47 (18.4) ‡	38 (14.2)	43 (16.7) ‡	25 (10.0)
	ACR/EUL AR Index Remission, n (%)	73 (28.5) ‡	60 (22.6)	58 (22.6)	41 (16.4)
	Week 52: ACR/EUL AR Boolean Remission, n (%)	59 (25.7) ‡	43 (18.7)	48 (21.1)	34 (15.5)
	ACR/EUL AR Index Remission, n (%)	83 (36.1) ‡	69 (30.0)	66 (29.3)	49 (22.4)

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

COV ID-19

Clinical Efficacy

RECOVERY (Randomised Evaluation of COVID-19 Therapy) Collaborative Group Study in Hospitalized Adults Diagnosed with COVID-19

RECOV ERY was a large, randomized, controlled, open-label, multi-center platform study conducted in the United K ingdom to evaluate the efficacy and safety of potential treatments in hospitalized adult patients with severe COV ID-19. All eligible patients received usual care and underwent an initial (main) randomization. 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 COV ID-19 (defined as oxygen saturation <92% on room air or receiving oxygen therapy, and CRP ≥75 mg/L) qualified for a second randomization 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 randomized 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 randomization). 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

sJIA Patients

Clinical efficacy

The efficacy of tocilizumab for the treatment of active sJIA was assessed in a 12 week randomized, double blind, placebo-controlled, parallel group, two

arm study. Patients included in the trial had a total disease duration of at least 6 months and active disease but were not experiencing an acute flare requiring corticosteroid doses of more than 0.5 mg/kg prednisone equivalent. Efficacy for the treatment of macrophage activation syndrome has not been investigated.
Patients (treated with or without MTX) were randomised (tocilizumab:placebo = 2:1) to one of two treatment groups, 75 patients received tocilizumab infusions every two weeks, either 8 mg/kg for patients ≥ 30 kg or 12 mg/kg for patients < 30 kg and 37 patients were assigned to receiving placebo infusions every two weeks. Corticosteroid tapering was permitted from week six for patients who achieved a JIA ACR70 response. After 12 weeks or at the time of escape, due to disease worsening, patients were treated in the open label phase at weight appropriate dosing.

Clinical response
The primary endpoint was the proportion of patients with at least 30% improvement in the JIA ACR core set (JIA ACR30 response) at week 12 and absence of fever (no temperature recording ≥ 37.5°C in the preceding 7 days). Eighty five percent (64/75) of tocilizumab treated patients and 24.3% (9/37) of placebo treated patients achieved this endpoint. These proportions were highly significantly different (p<0.0001).

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

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

R esponse R ate	T ocilizumab 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 V AS after 12 weeks of tocilizumab treatment was a reduction of 41 points on a scale of 0 - 100 compared to a reduction of 1 for placebo patients (p<0.0001).

Corticosteroid Tapering
Patients achieving a JIA ACR70 response were permitted corticosteroid dose reduction. Seventeen (24%) tocilizumab treated patients versus 1 (3%) placebo patient were able to reduce their dose of corticosteroid by at least 20% without experiencing a subsequent JIA ACR30 flare or occurrence of systemic symptoms to week 12 (p=0.028). Reductions in corticosteroids

continued, with 44 patients off oral corticosteroids at week 44, while maintaining JIA ACR responses.

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

Laboratory Parameters
Fifty out of seventy-five (67%) tocilizumab treated patients had a haemoglobin < L L N 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 < L L N at baseline (p<0.0001).

pJIA Patients
Clinical efficacy
The efficacy of tocilizumab was assessed in a three-part study WA19977 including an open-label extension in children with active pJIA. Part I consisted of a 16-week active tocilizumab treatment lead-in period (n=188) followed by Part II, a 24-week randomized double-blind placebo-controlled withdrawal period (n=163), followed by Part III, a 64-week open-label period. In Part 1, eligible patients ≥ 30 kg received tocilizumab at 8 mg/kg IV every 4 weeks for 4 doses. Patients < 30 kg were randomized 1:1 to receive either tocilizumab 8 mg/kg or 10 mg/kg IV every 4 weeks for 4 doses. Patients who completed Part I of the study and achieved at least a JIA ACR30 response at week 16 compared to baseline were eligible to enter the blinded withdrawal period (Part II) of the study. In Part II, patients were randomized to tocilizumab (same dose received in Part I) or placebo in a 1:1 ratio, stratified by concurrent MTX use and concurrent corticosteroid use. Each patient continued in Part II of the study until Week 40 or until the patient satisfied JIA ACR30 flare criteria (relative to Week 16) and qualified for escape to tocilizumab therapy (same dose received in Part I).

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

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

During the withdrawal phase (Part II), the percentage of patients achieving JIA ACR 30, 50, and 70 responses at Week 40 relative to baseline are shown in Table 9. In this statistical analysis, patients who flared (and escaped to TCZ) during Part II or who withdrew, were classified as non-responders. An additional analyses of JIA ACR responses, considering observed data at

Week 40, regardless of flare status, showed that by Week 40, 95.1% of patients who had received continuous TCZ therapy, had achieved JIA ACR30 or higher.

Table 9. JIA ACR Response Rates at Week 40 Relative to baseline (Percentage of Patients)

R esponse R ate	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 V AS 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 ACR30 Flare and Proportion of Patients with JIA ACR30/50/70/90 Responses at Week 40, by Previous Biologic Use (ITT Population - Study Part II)

	Placebo		All T C Z	
Biologic Use	Y es (N = 23)	No (N = 58)	Y es (N = 27)	No (N = 55)
JIA ACR30 Flare	18 (78.3)	21 (36.2)	12 (44.4)	9 (16.4)
JIA ACR30 Response	6 (26.1)	38 (65.5)	15 (55.6)	46 (83.6)
JIA ACR50 Response	5 (21.7)	37 (63.8)	14 (51.9)	46 (83.6)
JIA ACR70 Response	2 (8.7)	32 (55.2)	13 (48.1)	40 (72.7)
JIA ACR90 Response	2 (8.7)	17 (29.3)	5 (18.5)	32 (58.2)

Patients randomized to tocilizumab had fewer ACR30 flares and higher overall ACR responses than patients receiving placebo regardless of a history of prior biologic use.

CRS

The efficacy of RoActemra 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 lifethreatening 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 of RoActemra were needed, and no drugs other than RoActemra 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 RoActemra in all subsets of the paediatric population in treatment of cytokine release syndrome associated with chimeric antigen receptor (CAR) T cell therapy.

COV ID-19

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

5.2 Pharmacokinetic properties

Intravenous use

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) = 38000 ± 13000 h µg/mL , trough concentration (C_{min}) = 15.9 ± 13.1 mg/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) steadystate 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).

COV ID-19 Patients

The pharmacokinetics of tocilizumab was characterized using a population pharmacokinetic analysis of a database composed of 380 adult COV ID-19 patients in Study WA42380 (COV ACTA) 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 COV ID-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 noninvasive 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 COV ID-19 patients, serum concentrations were below the limit of quantification after 35 days on average following one infusion of tocilizumab IV 8 mg/kg.

L inearity

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 COV ID-19 patients, showed that age, gender and ethnic origin did not affect the pharmacokinetics of tocilizumab.

Results of the population PK analysis for COV ID-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 IV every 2 weeks (patients with a body weight ≥ 30 kg) 12 mg/kg IV every 2 weeks (patients with a body weight < 30 kg), 162 mg SC every week (patients weighing ≥ 30 kg), 162 mg SC every 10 days or every 2 weeks (patients weighing below 30 kg).

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

R oActemra PK Parameter	8 mg/kg Q2W ≥ 30 kg	12 mg/kg Q2W below 30 kg
C_{max} (µg/mL)	256 ± 60.8	274 ± 63.8
C_{trough} (µg/mL)	69.7 ± 29.1	68.4 ± 30.0

C_{mean} (µg/mL)	119 ± 36.0	123 ± 36.0
Accumulation C_{max}	1.42	1.37
Accumulation C_{trough}	3.20	3.41
Accumulation C_{mean} or AUC_{τ}*	2.01	1.95

*τ = 2 weeks for IV regimens

After IV dosing, approximately 90% of the steady-state was reached by week 8 for both the 12 mg/kg (BW < 30 kg) and 8 mg/kg Q2W (BW ≥ 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 characterized by a population pharmacokinetic analysis which included 237 patients who were treated with 8 mg/kg IV every 4 weeks (patients weighing ≥ 30 kg), 10 mg/kg IV every 4 weeks (patients weighing below 30 kg), 162 mg SC every 2 weeks (patients weighing ≥ 30 kg), or 162 mg SC every 3 weeks (patients weighing below 30 kg).
Table 12. Predicted mean ± SD PK parameters at steady-state after IV dosing in pJIA

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

*τ = 4 weeks for IV regimens

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

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

5.3 Preclinical safety data

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Polysorbate 80
Disodium phosphate dodecahydrate
Sodium dihydrogen phosphate dihydrate
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial: 30 months

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 30ºC 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 should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C–8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

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

For storage conditions of the diluted medicinal product see section 6.3.

6.5 Nature and contents of container

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 should be inspected visually for particulate matter or discolouration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted. Use a sterile needle and syringe to prepare RoActemra.

RA, CRS Patients (≥ 30 kg) and COV ID-19
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.

7. MARKETING AUTHORISATION HOLDER

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

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