ACTEMRA® IV Injection (Tocilizumab)

WARNING: To be sold by retail on prescription of specialist only

---

WARNINGS

1. Infections

Patients treated with **ACTEMRA** are at increased risk for developing serious infections (sepsis, pneumonia) that may lead to hospitalization or death *[see Warnings and Precautions, Undesirable Effects]*.

Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt **ACTEMRA** until the infection is controlled.

Reported infections include:

• Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before **ACTEMRA** use and during therapy. Treatment for latent infection should be initiated prior to **ACTEMRA** use.

• Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.

• Bacterial, viral and other infections due to opportunistic pathogens.

The risks and benefits of treatment with **ACTEMRA** should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

ACTEMRA exerts its therapeutic effects by inhibiting the activity of interleukin- 6 (IL-6), a cytokine that induces acute phase reactions (e.g. fever, increased C-reactive protein [CRP]). Treatment with **ACTEMRA** inhibits these reactions, thus suppressing the symptoms associated with infection. This may delay the detection of infections and cause them to become more serious. Carefully monitor and interview patients for signs of infections during **ACTEMRA** treatment. Even if symptoms are mild and no acute phase reactions are observed, closely monitor the patient for changes in white blood cell (WBC) and neutrophil counts. If infection is suspected, take appropriate measures such as performing a chest X-ray or CT scan.

2. Before **ACTEMRA** treatment, ensure that the patient has received and understood a sufficient explanation—including the fact that **ACTEMRA** may cause serious infection or other adverse reactions and that it may not completely cure the patient's disease and only administer **ACTEMRA** if the benefits of treatment outweigh the risks.

3. Carefully consider the use of at least one antirheumatic drug before starting **ACTEMRA** treatment. Moreover, **ACTEMRA** must be prescribed by a physician who has sufficient knowledge of **ACTEMRA** and who has experience in treating rheumatoid arthritis (RA) or active polyarticular-course juvenile idiopathic arthritis (pJIA).

4. **ACTEMRA** must be prescribed by a physician who has sufficient knowledge of **ACTEMRA** and who has experience in treating systemic juvenile idiopathic arthritis (sJIA).

1. Description

1.1 Therapeutic/Pharmacologic Class of Drug

Tocilizumab is a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass.

ATC Code: L04AC07.

1.2 Type of Dosage Form and Strengths

Dosage Form: Concentrate solution for infusion

Strength: 20 mg/ml

1.3 Route of Administration

Intravenous (IV) infusion

1.4 Sterile/Radioactive Statement

Sterile

1.5 Qualitative and Quantitative Composition

Active ingredient: tocilizumab

Excipients: Sucrose, Polysorbate 80, Disodium phosphate dodecahydrate, Sodium dihydrogen phosphate dihydrate and Water for injections

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

2. Clinical Particulars

2.1 Therapeutic Indications

For the following diseases which do not show sufficient response to the existing therapies:

- Rheumatoid arthritis (RA), (including inhibition of progression of structural joint damage)
- Polyarticular‑course juvenile idiopathic arthritis (pJIA),
- Systemic juvenile idiopathic arthritis (sJIA).
- Tocilizumab 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 (MTX).
- Improvement of various symptoms (e.g. generalised fatigue) and laboratory findings (increased C-reactive protein, fibrinogen, and erythrocyte sedimentation rate, decreased haemoglobin and albumin) associated with Castleman's disease.

2.2 Dosage and Administration

General

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

For adult patients with RA, tocilizumab may be administered as an IV infusion.

For patients with pJIA, sJIA and Castleman's disease, tocilizumab is administered as an IV infusion.

Tocilizumab IV formulation is not intended for subcutaneous administration.

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

Rheumatoid Arthritis [IV formulation]

Intravenous Dosing regimen

The recommended dose of Tocilizumab for adult patients is 8 mg/kg body weight, given once every four weeks as an IV infusion. Tocilizumab can be used alone or in combination with MTX and/or other DMARDs.

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

Dose Modification Recommendations for RA: (*see section 2.4.4 Laboratory Tests*)

- Liver enzyme abnormalities

Laboratory Value	Action
> 1 to 3 x Upper Limit of Normal (ULN)	Dose modify concomitant DMARDs (RA) if appropriate For patients on intravenous tocilizumab (RA only) with persistent increases in this range, reduce tocilizumab dose to 4 mg/kg or interrupt tocilizumab until alanine aminotransferase (ALT) or aspartate aminotransferase (AST) have normalized Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate.
> 3 to 5x ULN	Interrupt tocilizumab dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN For persistent increases > 3x ULN (confirmed by repeat testing, see section 2.4.4), discontinue tocilizumab
> 5x ULN	Discontinue tocilizumab

- Low absolute neutrophil count (ANC)

Laboratory Value (cells x 10^9/L)	Action
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt tocilizumab dosing For patients on intravenous tocilizumab (RA only), when ANC > 1 x 10^9/l resume tocilizumab at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
ANC < 0.5	Discontinue tocilizumab

- Low platelet count

Laboratory Value (cells x 10^3/mL)	Action
50 to 100	Interrupt tocilizumab dosing For patients on intravenous tocilizumab (RA only), when platelet count is > 100 x 10^3/mL resume tocilizumab at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
< 50	Discontinue tocilizumab

pJIA: The recommended dose of tocilizumab (genetical recombination) is 8 mg/kg as a single intravenous drip infusion administered at 4-week intervals.

sJIA and Castleman's disease: The recommended dose of tocilizumab (genetical recombination) is 8 mg/kg as a single intravenous drip infusion administered at 2-week intervals. The dosing interval can be shortened to a minimum of 1 week depending on the patient's disease condition.

Precautions related to dosage and administration for Castleman's disease: Measure CRP levels after each dose of **ACTEMRA** and only shorten the dosing interval if the patient's CRP levels indicate that the current dosage has not elicited sufficient improvement in the patient's symptoms

Precautions related to dosage and administration for sJIA: Only shorten the dosing interval if the current **ACTEMRA** dosage has not sufficiently improved the patient's symptoms and inhibited the action of IL-6 as indicated by C-reactive protein (CRP) levels.

2.2.1 Special Dosage Instructions

Children

The safety and efficacy of tocilizumab in children with conditions other than pJIA or sJIA have not been established. Children under the age of two have not been studied.

Elderly

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

Renal impairment

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

Hepatic impairment

The safety and efficacy of tocilizumab has not been studied in patients with hepatic impairment (see section 2.4.1 Warnings and Precautions, General).

2.3 Contraindications

ACTEMRA is contraindicated in patients with a known hypersensitivity to tocilizumab or to any of the excipients.

2.4 Warnings and Precautions

2.4.1 General

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

All Indications

Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including tocilizumab (see section 2.6, Undesirable Effects). Tocilizumab treatment should not be initiated in patients with active infections. Administration of tocilizumab should be interrupted if a patient develops a serious infection until the infection is controlled. Healthcare professionals should exercise caution when considering the use of tocilizumab in patients with a history of recurring infection or with underlying conditions (e.g. diverticulitis, diabetes) which may predispose patients to infections.

Vigilance for the timely detection of serious infection is recommended for patients receiving immunosuppressive agents, such as tocilizumab, as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute phase reactions. Patients (which include younger children who may be less able to communicate their symptoms) and parents/guardians of minors should be instructed to contact their healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

Complications of Diverticulitis

Events of diverticular perforation as complications of diverticulitis have been reported in patients treated with tocilizumab (see section 2.6 *Undesirable effects*). Tocilizumab should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, should be evaluated promptly for early identification of gastrointestinal perforation.

Tuberculosis

As recommended for other biologic therapies in all patients should be screened for latent tuberculosis infection prior to starting tocilizumab therapy. Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before initiating tocilizumab.

Vaccinations

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

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

In a randomized open-label study, adult RA patients treated with tocilizumab and MTX were able to mount an effective response to both the 23-valent pneumococcal polysaccharide and tetanus toxoid vaccines which was comparable to the response seen in patients on MTX only.

It is recommended that all patients, particularly pediatric or elderly patients, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating tocilizumab therapy. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis have been reported in association with tocilizumab (*see section 2.6 Undesirable Effects*). In the post marketing setting, events of serious hypersensitivity and anaphylaxis have occurred in patients treated with a range of doses of tocilizumab, with or without concomitant therapies, premedication, and / or a previous hypersensitivity reaction. In the post marketing setting, cases with a fatal outcome have been reported with intravenous tocilizumab. These events have occurred as early as the first infusion of tocilizumab (*see sections 2.3 Contraindications, 2.6.2 Post Marketing*).

Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during infusion with tocilizumab. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of tocilizumab should be stopped immediately and tocilizumab should be permanently discontinued (*see section 2.2 Dosage and Administration*).

Active Hepatic Disease and Hepatic Impairment

Treatment with tocilizumab particularly when administered concomitantly with methotrexate, 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 section *2.2.1 Special Dosage Instructions*, 2.6 *Undesirable Effects*).

Hepatotoxicity

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

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

Caution should be exercised when considering initiation of tocilizumab treatment in patients with elevated transaminases ALT or AST above 1.5x ULN. In patients with elevated ALT or AST above 5x ULN treatment is not recommended.

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

Viral reactivation

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

Demyelinating disorders

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

Neutropenia

Treatment with tocilizumab was associated with a higher incidence of neutropenia. Treatment-related neutropenia was not associated with serious infection in clinical trials (*see section 2.6.1.1 Laboratory Abnormalities*).

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

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

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

Thrombocytopenia

Treatment with tocilizumab was associated with a reduction in platelet counts. Treatment-related reduction in platelets was not associated with serious bleeding events in clinical trials (*see section 2.6.1.1 Laboratory Abnormalities*).

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

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

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

Lipids parameters

Elevations of lipid parameters such as total cholesterol, triglycerides and/or low density lipoprotein (LDL) cholesterol have been observed (*see section 2.6.1.1 Laboratory Abnormalities*).

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

sJIA and Castleman's disease:

Interrupting or discontinuing **ACTEMRA** treatment may lead to disease exacerbation due to overexpression of IL-6. Consider adding or increasing the dose of corticosteroids or other appropriate measures as required.

sJIA

Macrophage activation syndrome (MAS)

MAS is a serious life-threatening disorder that may develop in patients with sJIA. In clinical trials,

tocilizumab has not been studied in patients during an episode of active MAS.

In patients with concurrent MAS, prioritize the treatment of this complication and do not initiate treatment with **ACTEMRA**. If the patient develops MAS while receiving **ACTEMRA**, discontinue **ACTEMRA** and immediately treat the MAS appropriately.

2.4.2 Drug Abuse and Dependence

No studies on the effects on the potential for tocilizumab to cause dependence have been performed. However, there is no evidence from the available data that tocilizumab treatment results in dependence.

2.4.3 Ability to Drive and Use Machines

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

2.5 Use in Special Populations

2.5.1 Pregnancy

There are no adequate data from the use of tocilizumab in pregnant women. A study in monkeys did not indicate any dysmorphogenic potential but has yielded a higher number of spontaneous abortion/embryo-foetal death at a high dose (see section 3.3 Pre-clinical Safety). The relevance of these data for humans is unknown.

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

2.5.2 Labor and Delivery

No text

2.5.3 Nursing Mothers

It is unknown whether tocilizumab is excreted in human breast milk. Although endogenous immunoglobulins of the IgG isotope are secreted into human milk, a systemic absorption of tocilizumab via breast feeding is unlikely due to the rapid proteolytic degradation of such proteins in the digestive system. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with tocilizumab should be made taking into account the benefit of breast-feeding to the child and the benefit of tocilizumab therapy to the woman.

2.5.4 Paediatric Use

(See section 2.2.1 Special Dosage Instructions).

2.5.5 Geriatric Use

(See section 2.2.1 Special Dosage Instructions, section 3.2.5 Pharmacokinetics in Special Populations).

2.5.6 Renal Impairment

(See section 2.2.1 Special Dosage Instructions, section 3.2.5 Pharmacokinetics in Special

Populations).

2.5.7 Hepatic Impairment

(See section 2.2.1 Special Dosage Instructions, section 3.2.5 Pharmacokinetics in Special Populations).

2.6 Undesirable Effects

2.6.1 Clinical Trials

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

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

Table 1: Summary of ADRs occurring in patients treated with Tocilizumab

System Organ Class	Very Common	Common	Uncommon
Infections and infestations	Upper respiratory tract infections	Cellulitis, Oral herpes simplex, Herpes zoster	Diverticulitis
Gastrointestinal disorders		Abdominal pain, Mouth ulceration, Gastritis	Stomatitis, Gastric ulcer
Skin and subcutaneous tissue disorders		Rash, Pruritus, Urticaria	
Nervous system disorders		Headache, Dizziness	
Investigations		Hepatic transaminases increased, Weight increased,	Total bilirubin increased
Vascular disorders		Hypertension	
Blood and lymphatic system disorders		Leukopenia, Neutropenia	
Metabolism and nutrition disorders		Hypercholesterolaemia	Hypertriglyceridaemia
General disorders and administration site conditions		Peripheral oedema Hypersensitivity reactions, Injection site reaction	

Respiratory, thoracic and mediastinal disorders		Cough, Dyspnoea	
Eye disorders		Conjunctivitis	
Renal disorders			Nephrolithiasis
Endocrine disorders			Hypothyroidism

Description of selected adverse drug reactions from clinical trials

Rheumatoid Arthritis

Patients Treated with Intravenous Tocilizumab:

The safety of tocilizumab has been studied in 5 Phase III, double-blind controlled trials and their extension periods.

The *all control* population includes all patients from the double-blind phases of each core study from randomization until either the first change in the treatment regimen, or two years is reached. The control period in 4 of the studies was 6 months and in 1 study was up to 2 years. In the double-blind controlled studies, 774 patients received tocilizumab 4 mg/kg in combination with MTX, 1870 patients received Tocilizumab 8 mg/kg in combination with MTX/other DMARDs, and 288 patients received tocilizumab 8 mg/kg monotherapy.

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

Infections

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

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

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

Gastrointestinal Perforation

During the 6-month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 pt years with tocilizumab therapy. In the *all exposure* population the overall rate of

gastrointestinal perforation was 0.28 events per 100 pt years. Reports of gastrointestinal perforation on tocilizumab were primarily reported as complications of diverticulitis including generalized purulent peritonitis, lower GI perforation, fistula and abscess.

Infusion Reactions

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

The rate of anaphylactic reactions (occurring in a total of 6/3778 patients) was several-fold higher in the 4 mg/kg arm in comparison to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation, were reported in a total of 13 out of 3778 patients (0.3%) treated with tocilizumab during the controlled and open label clinical trials. These reactions were generally observed during the second to fifth infusions of tocilizumab (*see section 2.4.1 Warnings and Precautions, General*).

Immunogenicity

A total of 2876 patients have been tested for anti-tocilizumab antibodies in the 6-month controlled clinical trials. Forty-six patients (1.6%) developed positive anti-tocilizumab antibodies of whom 5 had an associated medically significant hypersensitivity reaction leading to withdrawal. Thirty patients (1.1%) developed neutralising antibodies.

Early Rheumatoid Arthritis

Study VI (WA19926) evaluated 1162 patients with early, moderate to severe RA who were naïve to treatment with both MTX and a biologic agent. The overall safety profile observed in the tocilizumab treatment groups was consistent with the known safety profile of tocilizumab (see Table 1) (*see section 3.2 Clinical/Efficacy Studies*).

Monotherapy: Tocilizumab versus Adalimumab

In a 24-week double-blinded, parallel study (monotherapy with tocilizumab 8 mg/kg IV q4w (N=162) compared to adalimumab 40 mg SC q2w (N=162)), 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%) with the most common event being infections (3.1% each). Both study treatments induced the same pattern of changes in laboratory safety parameters (decreases in neutrophil and platelet counts, increases in ALT, AST and lipids), however, the magnitude of change and the frequency of marked abnormalities was higher with tocilizumab compared with adalimumab. Four (2.5%) patients in the tocilizumab arm and two (1.2%) patients in the adalimumab arm experienced CTC grade 3 or 4 neutrophil count decreases. Eleven (6.8%) patients in the tocilizumab arm and five (3.1%) patients in the adalimumab arm experienced ALT increases of CTC grade 2 or higher. The mean LDL increase from baseline was 0.64 mmol/L (25 mg/dL) for patients in the tocilizumab arm and 0.19 mmol/l (7 mg/dL) for patients in the adalimumab arm. The safety observed in the tocilizumab arm was consistent with the known safety profile of tocilizumab and no new or unexpected adverse drug reactions were observed (see Table 1) (*see section 3.1.2 Clinical/Efficacy Studies*).

Patients Treated with Subcutaneous Tocilizumab

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

Injection Site Reactions (ISRs)

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

Immunogenicity

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

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

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

Giant Cell Arteritis

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

Infections

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

Polyarticular Juvenile Idiopathic Arthritis

The safety profile of tocilizumab was studied in 240 paediatric patients with pJIA. In Study WA19977, 188 patients (2 to 17 years of age) were treated with IV tocilizumab and in Study WA28117, 52 patients (1 to 17 years of age) were treated with SC tocilizumab. The total patient exposure to tocilizumab in the pJIA all exposure population was 184.4 patient years for IV tocilizumab and 50.4 patient years for SC tocilizumab. In general, the safety profile observed in patients with pJIA was consistent with the known safety profile of tocilizumab with the exception of ISRs (see Table 1). A higher frequency of ISRs was experienced by pJIA patients following SC tocilizumab injections compared to adult RA patients (see Undesirable Effects section).

Infections

Infections are the most commonly observed events in pJIA. The rate of infections in the pJIA IV 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 below 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 below 30 kg treated with 10 mg/kg tocilizumab (21.4%) compared to patients weighing ≥30 kg, treated with 8 mg/kg tocilizumab (7.6%). The rate of infection in pJIA patients treated with SC tocilizumab was comparable with pJIA patients treated with IV tocilizumab.

Infusion Reactions

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

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

Injection Site Reactions

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

Immunogenicity

Across the two studies in pJIA patients, a total of four patients (0.5% [1/188] in the IV Study WA19977 and 5.8% [3/52] in the SC Study WA28117) developed positive neutralizing anti-tocilizumab antibodies without developing a serious or clinically significant hypersensitivity reaction. Of these 4 patients, 2 subsequently withdrew from the study. No correlation between antibody development and clinical response or adverse events was observed.

Systemic Juvenile Idiopathic Arthritis

The safety profile of tocilizumab in sJIA was studied in 163 paediatric patients. In Study WA18221 (12-week trial and long term extension), 112 patients (2 to 17 years of age) were treated with IV tocilizumab and in Study WA28118 (52-week trial), 51 patients (1 to 17 years of age) were treated with SC tocilizumab.

In general, the adverse drug reactions in patients with sJIA were similar in type to those seen in RA patients (see Undesirable Effects section above).

Infections

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

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

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

Infusion Reactions

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

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

Injection Site Reactions (ISRs)

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

Immunogenicity

In Study WA18221, all 112 patients were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti-tocilizumab antibodies with one of these patients having a hypersensitivity reaction leading to withdrawal. In Study WA28118, 46 of the 51 (90.2%) patients tested for anti-tocilizumab antibodies at baseline had at least one post-baseline screening assay result. No patient developed positive anti-tocilizumab antibodies post-baseline.

Laboratory Abnormalities

Haematology Abnormalities:

Neutrophils

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

Rheumatoid Arthritis

Intravenous Administration:

In the 6-month controlled trials decreases in neutrophil counts below $1 \times 10^9/L$ occurred in 3.4% of patients on tocilizumab 8 mg/kg + DMARD compared to below 0.1% of patients on placebo + DMARD. Approximately half of the instances of ANC below $1 \times 10^9/L$ occurred within 8 weeks after starting therapy. Decreases below $0.5 \times 10^9/L$ were reported in 0.3% patients receiving tocilizumab 8 mg/kg + DMARD (*see sections 2.2 Dosage and Administration, 2.4.4 Laboratory Tests*).

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

Subcutaneous Administration

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

Giant Cell Arteritis

During routine laboratory monitoring in the tocilizumab 12-month double blind, placebo-controlled phase of study WA28119, a decrease in neutrophil count below $1 \times 10^9/L$ occurred in 4% of patients in the tocilizumab SC weekly group. This was not observed in either of the placebo plus prednisone taper groups.

Polyarticular Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the tocilizumab all exposure population, a decrease in neutrophil count below $1 \times 10^9/L$ occurred in 3.7% of patients treated with IV tocilizumab and 15.4% of patients treated with SC tocilizumab.

Systemic Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the 12-week controlled trial (Study WA18221), a decrease in neutrophil counts below $1 \times 10^9/L$ occurred in 7% of patients in the IV tocilizumab group, and in none in the placebo group.

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

In the 52-week open-label trial (Study WA28118), neutrophil count decrease below $1 \times 10^9/L$ occurred in 23.5% of patients treated with SC tocilizumab.

Platelets

Rheumatoid Arthritis

Intravenous Administration:

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

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

Subcutaneous Administration

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

Giant Cell Arteritis

During routine laboratory monitoring in the tocilizumab 12-month double blind, placebo controlled phase of study WA28119, one patient (1%, 1/100) in the tocilizumab SC weekly group had a single transient occurrence of decreased platelet count below 100 x 10^3 / μL without associated bleeding events. A decrease in platelet count below 100 x 10^3 / μL was not observed in either of the placebo plus prednisone taper groups.

Polyarticular Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the tocilizumab all exposure population, a decrease in platelet count to ꓳ50 × 10^3 / μL occurred in 1% patients treated with IV tocilizumab, without associated bleeding events and in no patients treated with SC tocilizumab.

Systemic Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the 12-week controlled trial (Study WA18221), 3% of patients in the placebo group and 1% in the IV tocilizumab group had a decrease in platelet count to ꓳ 100 × 10^3 / μL.

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

In the 52-week open-label trial (Study WA28118), decreases in platelet counts below 100 × 10^3 / μL occurred in 2% of patients treated with SC tocilizumab.

Liver Enzyme Elevations

Rheumatoid Arthritis

Intravenous Administration:

During the 6-month controlled trials transient elevations in ALT/AST above 3 x ULN were observed in 2.1% of patients on tocilizumab 8 mg/kg compared to 4.9% of patients on MTX, and in 6.5% of patients who received tocilizumab 8 mg/kg + DMARD compared to 1.5% of patients on placebo + DMARDs. The addition of potentially hepatotoxic drugs (e.g. MTX) to tocilizumab monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST above 5 x ULN were observed in 0.7% of tocilizumab monotherapy patients and 1.4% of tocilizumab + DMARD patients, the majority of whom were discontinued from tocilizumab treatment (*see section 2.2 Dosage and Administration, 2.4.4 Laboratory Tests*). During routine laboratory monitoring, the incidence of indirect bilirubin greater than the upper limit of normal was 6.2% in patients treated with 8 mg/kg Tocilizumab + DMARD in the *all control* population.

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

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

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

Subcutaneous Administration:

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

Giant Cell Arteritis

During routine laboratory monitoring in the tocilizumab 12-month double blind, placebo-controlled phase of study WA28119, elevation in ALT ≥3 ULN occurred in 3% of patients in the tocilizumab SC weekly group compared to 2% in the placebo plus 52 week prednisone taper group and none in the placebo plus 26 weeks prednisone taper group. An elevation in AST > 3 ULN occurred in 1% of patients in the tocilizumab SC weekly group, compared to no patients in either of the placebo plus prednisone taper group.

Polyarticular Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the tocilizumab all exposure population, elevation in ALT or AST ≥3 x ULN occurred in 3.7% and below 1% of patients treated with IV tocilizumab, and in 9.6% and 3.8% patients treated with SC tocilizumab, respectively.

Systemic Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the 12 week controlled trial (Study WA18221), elevation in ALT or AST ≥ 3xULN occurred in 5% and 3% of patients, respectively, in the IV tocilizumab group, and in 0% of placebo patients.

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

In the 52-week open-label trial (Study WA28118), elevation in ALT or AST ≥3 x ULN occurred in 9.8% and 4.0% patients treated with SC tocilizumab, respectively.

Elevations in Lipid parameters

Rheumatoid Arthritis

Intravenous Administration:

During routine laboratory monitoring in the 6 month controlled trials, elevations in lipid parameters (total cholesterol, LDL, HDL, triglycerides) were observed in patients treated with tocilizumab. Approximately 24% of patients receiving tocilizumab in clinical trials experienced sustained

elevations in total cholesterol above 6.2 mmol/ L (240 mg/dL), with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/ L (160 mg/dL).

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

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

Subcutaneous Administration

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

Giant Cell Arteritis

During routine laboratory monitoring in the tocilizumab 12-month double blind, placebo-controlled phase of study WA28119, 29% of patients experienced elevations in total cholesterol above 6.2 mmol/L (240 mg/dL), with 12% experiencing an increase in LDL to ≥ 4.1 mmol/L (160 mg/dL) in the tocilizumab SC weekly group.

Polyarticular Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the IV tocilizumab Study WA19977 3.4 % and 10.4% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL at any time during the study treatment, respectively. In the SC tocilizumab Study WA28117, 14.3% and 12.8% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL at any time during study treatment, respectively.

Systemic Juvenile Idiopathic Arthritis

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

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

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

From Japanese Studies in RA, pJIA, sJIA, Castleman's disease

The following adverse reactions may occur. Closely monitor patients and if any abnormalities are observed, take appropriate measures such as discontinuing treatment.

(1) Clinically significant adverse reactions

1) **Anaphylactic shock** (0.1%) **or anaphylaxis** (0.1 %): Decreased blood pressure, dyspnoea, loss of consciousness, dizziness, nausea, vomiting, pruritus, flushing and other reactions may occur. If any abnormalities are observed, immediately discontinue **ACTEMRA** treatment, take appropriate measures such as administering adrenaline, corticosteroids, or antihistamines, and closely monitor the patient until symptoms resolve.

2) **Infections**: **ACTEMRA** may cause serious infections including opportunistic infections, some with fatal outcome, such as pneumonia [3.3%], herpes zoster [2.0 %], infectious enteritis [0.7%], cellulitis [1.4%], infectious arthritis [0.5%], sepsis [0.6%], nontuberculous mycobacteriosis [0.4%], tuberculosis [0.1%], and Pneumocystis pneumonia [0.3%].

3) **Interstitial pneumonia** (0.5%): In patients with rheumatoid arthritis, closely monitor their condition for fever, cough, dyspnea, and other respiratory symptoms. If any abnormality is observed, promptly perform relevant tests such as chest X-ray, CT scan or blood gas analysis, the discontinue **ACTEMRA** treatment and take appropriate measures incorporating the findings of differential diagnosis of pneumocystis pneumonia (beta-D-glucan assay, etc.).

4) **Intestinal perforation** (0.2%): Treatment with **ACTEMRA** inhibits acute phase symptoms of diverticulitis (abdominal pain, fever, etc.). This inhibitory effect could delay detection of these symptoms and lead to intestinal perforation. Therefore, if any abnormalities are observed, closely monitor patients such as by performing examinations such as chest X-rays and CT scans, and take appropriate measures.

5) **Agranulocytosis** (<0.1%), **decreased white blood cell count** (4.5%), **decreased neutrophil count** (1.6%) **and decreased platelet count** (2.1%): **ACTEMRA** may cause further decreases in white blood cells, neutrophils, and platelets.

6) **Cardiac failure** (0.2%)

Cardiac disorders have been observed in clinical studies of **ACTEMRA**. Carefully monitor patients and perform electrocardiogram (ECG), blood tests, chest ultrasound, or other relevant tests as required. Perform routine ECGs and monitor any changes.

7) **Hepatic impairment** (frequency unknown): Hepatic impairment with increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin, etc., may occur.

(2) Other adverse drug reactions

	³1%*	0.1% to <1%*	<0.1%*
Resistance mechanism	Herpes virus infection	Influenza, oral candidiasis, parotitis, wound infection	
Respiratory	Upper respiratory tract infection [Nasopharyngitis, upper respiratory tract inflammation, etc.] (10.7%), bronchitis, pharyngolaryngeal pain	Cough, sinusitis, rhinitis, rhinorrhoea, pleurisy, haemoptysis, asthma, pharynx discomfort, pharyngeal erythema, nasal congestion, epistaxis	Bronchiectasis
Metabolic	increased Cholesterol (4.9 %), increased triglycerides, hyperlipidaemia, hypercholesterolaemia, increased low density lipoprotein (LDL)	Increased Blood lactate dehydrogenase, Increased high density lipoprotein , hypertriglyceridaemia, Increased blood uric acid , Increased creatine phosphokinase , decreased total protein , aggravated diabetes mellitus, decreased blood potassium, increased blood sugar, increased blood phosphorus, decreased serum ferritin	Decreased Blood phosphorus, Decreased blood calcium
Hepatic	Abnormal hepatic function , increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST)	Increased Gammaglutamyltransferase(γ-GTP) , increased bilirubin, increased alkaline phosphatase, hepatic steatosis, cholelithiasis	
Cardiovascular	Hypertension	Increased Blood pressure, decreased blood pressure, palpitations, T wave inversion/, decreased T wave amplitude, supraventicular extrasystoles, ventricular extrasystoles	ST segment elevation/, ST segment depression, increased T wave amplitude

	³1%*	0.1% to <1%*	<0.1%*
Resistance mechanism	Herpes virus infection	Influenza, oral candidiasis, parotitis, wound infection	
Respiratory	Upper respiratory tract infection [Nasopharyngitis, upper respiratory tract inflammation, etc.] (10.7%), bronchitis, pharyngolaryngeal pain	Cough, sinusitis, rhinitis, rhinorrhoea, pleurisy, haemoptysis, asthma, pharynx discomfort, pharyngeal erythema, nasal congestion, epistaxis	Bronchiectasis
Metabolic	increased Cholesterol (4.9 %), increased triglycerides, hyperlipidaemia, hypercholesterolaemia, increased low density lipoprotein (LDL)	Increased Blood lactate dehydrogenase, Increased high density lipoprotein , hypertriglyceridaemia, Increased blood uric acid , Increased creatine phosphokinase , decreased total protein , aggravated diabetes mellitus, decreased blood potassium, increased blood sugar, increased blood phosphorus, decreased serum ferritin	Decreased Blood phosphorus, Decreased blood calcium
Hepatic	Abnormal hepatic function , increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST)	Increased Gammaglutamyltransferase(γ-GTP) , increased bilirubin, increased alkaline phosphatase, hepatic steatosis, cholelithiasis	
Cardiovascular	Hypertension	Increased Blood pressure, decreased blood pressure, palpitations, T wave inversion‡, decreased T wave amplitude, supraventicular extrasystoles, ventricular extrasystoles	ST segment elevation‡, ST segment depression, increased T wave amplitude
Hematologic/Coagulatory		decreased Lymphocyte count, Anaemia, increased white blood cell count, decreased fibrinogen, increased eosinophil count, increased fibrin degradation products [FDP, D dimer], decreased haematocrit, decreased haemoglobin, lymphadenitis, swollen lymph nodes, increased neutrophil count, decreased red blood cell count	Thrombin-antithrombin III complex increased
Gastrointestinal	Stomatitis, diarrhea, gastroenteritis, abdominal pain	Nausea, constipation, vomiting, abdominal discomfort, cheilitis, abdominal distension, anorexia, gastric/colonic polyp, reflux oesophagitis, haemorrhoids, dyspepsia, glossitis, gastric ulcer, acute pancreatitis	Thirst
Psychoneurologic	Headache	Periodontal disease, dental caries, toothache Dizziness, hypoaesthesia, insomnia, peripheral neuropathy	
Auricular		Otitis media, vertigo, sudden hearing loss, otitis externa, tinnitus	Ear discomfort
Ocular		Conjunctivitis, hordeolum, dry eye, conjunctival haemorrhage, chalazion, cataract, blepharitis	Vitreous floaters, retinal haemorrhage
Dermatologic	Rash [eczema, prurigo, papule, etc.], pruritus, tinea, skin infection	Nail infection, urticaria, erythema, skin ulcer, haemorrhage subcutaneous, in growing nail, acne, dry skin, blister, keratosis, alopecia, dermal cyst	

	≥1%*	0.1% to <1%*	<0.1%*
Resistance mechanism	Herpes virus infection	Influenza, oral candidiasis, dermatitis, lymph node infection, Anal abscess, wound infection	
Respiratory	Upper respiratory tract infection [Nasopharyngitis, upper respiratory tract inflammation, etc.] (10.7%), bronchitis, pharyngolaryngeal pain	Cough, sinusitis, white blood cell count decreased, fibrinogen, haemoptysis, asthma, pharynx disorder, dyspnea, pneumonia, nasal congestion, rhinitis	Bronchiectasis
Hematologic/Coagulatory		decreased haemoglobin, decreased neutrophil count, lymphadenitis, swollen lymph nodes, increased red blood cell count	Thrombin-antithrombin III complex increased
Metabolic	increased Cholesterol (4.9 %), increased triglycerides, hyperlipidaemia, hypercholesterolaemia, increased low density lipoprotein (LDL)	decreased total protein, aggravated diabetes mellitus, decreased blood phosphorus, decreased blood albumin, increased uric acid	Decreased Blood phosphorus, Decreased blood calcium
Gastrointestinal	Stomatitis, diarrhea, gastroenteritis, abdominal pain	Nausea, constipation, vomiting, abdominal discomfort, stomatitis, gastritis, gastroenteritis, gastric ulcer, dyspepsia, gastritis, aphthous stomatitis	Thirst
Hepatic	Abnormal hepatic function , increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST)	Periodontal disease, dental caries, Gammaglutamyltransferase(γ-GTP), increased bilirubin, increased alkaline phosphatase, hepatic steatosis, cholelithiasis	
Psychoneurologic	Headache		
Auricular		Otitis media, vertigo, sudden deafness, Blood pressure increased, decreased blood pressure	Ear discomfort
Cardiovascular	Hypertension	palpitations, T wave inversion, decreased T wave amplitude, supraventricular extrasystoles, ventricular extrasystoles	ST segment elevation, ST segment depression, decreased T wave amplitude
Ocular		Conjunctivitis, blepharitis, dry eye, conjunctival haemorrhage, chalazion, cataract, blepharitis	vitreous floaters, retinal haemorrhage
Dermatologic	Rash [eczema, prurigo, papule, etc.], pruritus, tinea, skin infection	Nail infection, urticaria, erythema, skin ulcer, haemorrhage subcutaneous, in growing nail, acne, dry skin, blister, keratosis, alopecia, dermal cyst	
Musculoskeletal		Arthralgia, back pain, myalgia [myalgia, Stiff shoulder muscle], pain in extremity, osteoporosis, decreased bone density, neck pain, juvenile arthritis aggravated	
Urinary		Cystitis, urinary tract infection, increased blood urea nitrogen, red blood cells urine positive, pyelonephritis, sugar urinary , protein urine, nephrolithiasis, increased N-acetyl glucosamine (NAG), , pollakiuria	White blood cells urine positive
Reproductive		Vaginal infection, genital haemorrhage	Cervical polyp
Others	Abscess, pyrexia	Edema, malaise, decreased immunoglobulin G, chest pain, chest discomfort, seasonal allergy, increased C-reactive protein, chills, flushing, rhinitis allergic, feeling bad, hot flush, injection site reaction (erythema, swelling, haematoma, pain, phlebitis, rash, etc.), thrombophlebitis, DNA antibody positive**), increased weight , antinuclear antibody positive**)	Rheumatoid factor positive, dyshidrosis

In two Phase III studies in patients with RA, evaluation of conversion from baseline DNA antibody serostatus in 217 patients showed that 10 patients (4.6%) converted to seronegative DNA antibody titers and no patients converted to seropositive DNA antibody titers. Evaluation of conversion from baseline antinuclear antibody serostatus in 216 patients showed that 24 patients (11.1%) converted to seronegative status and 18 patients (8.3%) converted to seropositive status.

**Adverse reaction frequencies include data from post-marketing surveillance*

2.6.2 Post Marketing Experience

The following adverse drug reactions have been identified from post marketing experience with tocilizumab (Table 2) based on spontaneous case reports, literature cases and cases from non-interventional study programs. Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 2: Adverse drug reactions from post marketing experience

Adverse reaction (MedDRA)	Incidence[4]	Frequency Category
Immune System Disorders		
Anaphylaxis (fatal)[1,2]	Not observed in clinical trials	Rare
Skin and Subcutaneous Tissue Disorders		
Stevens-Johnson syndrome[3]	Not observed in clinical trials	Rare
Blood and lymphatic system disorders		
Hypofibrinogenemia	1.3 per 100 patient years	Common
Hepatobiliary disorders		
Drug-induced liver injury	0.027 per 100 patient years	Rare
Hepatitis	0.035 per 100 patient years	Rare
Hepatic failure	0.004 per 100 patient years	Very Rare
Jaundice[3]	Not observed in clinical trials	Rare

[1] *See section 2.3 Contraindications*

[2] *See section 2.4.1 Warnings and Precautions, General*

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

[4] *Incidence rate calculated based on all-exposure data obtained from relevant completed clinical trials for all indications.*

2.7 Overdose

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

2.8 Interactions with Other Medicinal Products and Other Forms of Interaction

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

Concomitant administration of a single dose of 10 mg/kg tocilizumab with 10-25 mg MTX once

weekly had no clinically significant effect on MTX exposure.

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

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

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

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

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

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

3. Pharmacological Properties and Effects

3.1 Pharmacodynamic Properties

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

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 2.4.4 Laboratory Tests*).

3.1.1 Mechanism of Action

Tocilizumab is a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass. Tocilizumab binds to both soluble and membrane-bound IL 6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit sIL-6R and mIL-6R-mediated signaling. IL-6 is a multifunctional cytokine, produced by a variety of cell types involved in local paracrine function as well as regulation of systemic physiological and pathological processes such as induction of immunoglobulin secretion, T-cell activation, induction of hepatic acute phase proteins and stimulation of haematopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis, and neoplasia.

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

3.1.2 Clinical / Efficacy Studies

Rheumatoid Arthritis

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

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

Study I evaluated 673 patients who had not been treated with MTX within 6 months prior to 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 8 week period). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Study II, a 2-year study, evaluated 1196 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of tocilizumab or placebo were given every four weeks as blinded therapy for 52 weeks, in combination with stable MTX (10 - 25 mg weekly). The primary endpoint at week 24 was the proportion of patients who achieved an ACR 20 response criteria. At week 52 the co-primary endpoints were prevention of joint damage and improvement in physical function.

Study III evaluated 623 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg tocilizumab or placebo were given every four weeks, in combination with stable MTX (10 - 25 mg weekly). Study IV evaluated 1220 patients who had an inadequate response to their existing rheumatologic therapy, including one or more DMARDs. Doses of 8 mg/kg tocilizumab or placebo were given every four weeks, in combination with the stable DMARD. Study V evaluated 499 patients who had an inadequate clinical response or were intolerant to one or more anti-TNF therapies. The anti-TNF agent was discontinued prior to randomisation. Doses of 4 or 8 mg/kg of tocilizumab or placebo were given every four weeks, in combination with stable MTX (10 - 25 mg weekly). The primary endpoint for studies III-V was the proportion of patients who achieved an ACR20 response at week 24.

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

Table 3: ACR responses in MTX/ Placebo Controlled Trials (Percent of Patients)

	Study I MTX-Naïve	Study II Inadequate Response to MTX	Study III Inadequate Response to MTX	Study IV Inadequate Response to DMARD	Study V Inadequate Response to TNF Blocking Agent

Response Rate	TCZ 8 mg/kg N=286	MTX N=284	TCZ 8 mg/kg +MTX N= 398	Placebo + MTX N=393	TCZ 8 mg/kg +MTX N= 205	Placebo + MTX N=204	TCZ 8 mg/kg + DMARD N=803	Placebo + DMARD N=413	TCZ 8 mg/kg +MTX N=170	Placebo + MTX N=158
ACR20										
Week 24	70%***	52%	56%***	27%	59%***	26%	61%***	24%	50%***	10%
Week 52			56%***	25%						
ACR50										
Week 24	44%**	33%	32%***	10%	44%***	11%	38%***	9%	29%***	4%
Week 52			36 %***	10%						
ACR70										
Week 24	28%**	15%	13%***	2%	22%***	2%	21%***	3%	12%**	1%
Week 52			20%***	4%						
MCR† by week 52			7%	1%						

TCZ = tocilizumab

* *p<0.05, tocilizumab vs. placebo+MTX/DMARD*

** *p<0.01, tocilizumab vs. placebo+MTX/DMARD*

*** *p<0.0001, tocilizumab vs. placebo+MTX/DMARD*

† *MCR = major clinical response, defined as an ACR70 response maintained for any 24 consecutive weeks or more.*

In all studies, 8 mg/kg tocilizumab-treated patients had statistically significant higher ACR 20, 50, 70 response rates at 6 months compared to control (Table 3). 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 of Studies I – V.

In the 8 mg/kg tocilizumab-treated patients significant improvements were noted on all individual components of the ACR response (tender and swollen joint counts, patient and physician global assessment, disability index scores (HAQ), pain assessment and CRP compared to patients receiving placebo +MTX/DMARDs in all studies.

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

Table 4: Cross-Study comparison of DAS and EULAR responses at Week 24

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

TCZ = tocilizumab

†The p value compares across all the EULAR categories

* p<0.05, tocilizumab vs. placebo+MTX/DMARD

** p<0.01, tocilizumab vs. placebo+MTX/DMARD

*** p<0.0001, tocilizumab vs. placebo+MTX/DMARD

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

Major Clinical Response

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

Radiographic response – Intravenous administration

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

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

Table 5: Radiographic mean changes over 52 and 104 weeks in Study II

	PBO + MTX (+option of TCZ from week 16)	TCZ 8 mg/kg + MTX
Changes from baseline to Week 52		
n	294	353
Total Sharp-Genant score	1.17	0.25
Erosion score	0.76	0.15
JSN score	0.41	0.10

Change from week 52 to week104		
n	294	353
Total Sharp-Genant score	0.79	0.12
Erosion score	0.48	0.07
JSN score	0.31	0.05

PBO - Placebo

MTX - Methotrexate

TCZ Tocilizumab

JSN - Joint space narrowing

All data presented was read together in campaign 2 which consists of the evaluations of the baseline, week 24, week 52, week 80, week 104 and early withdrawal or escape therapy readings taken up to week 104 visit

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

Quality of life outcomes – Intravenous administration

Clinically significant improvements in disability index (HAQ-DI, Health Assessment Questionnaire Disability Index), fatigue (FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy Fatigue) and improvement in both the physical (PCS, Physical Component Summary) and mental health (MCS, Mental Component Summary) domains of the SF-36 (Short Form 36) were observed in patients treated with 8 mg/kg tocilizumab (monotherapy or combination with DMARDs) compared to patients treated with MTX/DMARDs (Table 6).

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

Table 6 : Comparison of SF-36, HAQ and FACIT-Fatigue Responses at Week 24

Study I MTX-Naïve		Study II Inadequate Response to MTX		Study III Inadequate Response to MTX		Study IV Inadequate Response to DMARD		Study V Inadequate Response to TNF Blocking Agent	
TCZ 8 mg/kg N=286	MTX N=284	TCZ 8 mg/kg +MTX N= 398	Placebo + MTX N=393	TCZ 8 mg/kg +MTX N= 205	Placebo + MTX N=204	TCZ 8 mg/kg + DMARD N= 803	Placebo +DMARD N=413	TCZ 8 mg/kg +MTX N=170	Placebo + MTX N=158
Change in PCS [mean (Adjusted mean (SE))]									
10.2 (0.7)	8.4 (0.7)	8.1 (0.6)**	5.6 (0.7)	9.5 (0.8)***	5.0 (1.0)	8.9 (0.4)***	4.1 (0.6)	8.0 (0.9)**	2.2 (1.3)

Change in MCS [mean (Adjusted mean (SE))]									
6.7 (0.9)	5.0 (0.9)	4.2 (0.8)	2.8 (0.9)	7.3 (1.1)**	2.7 (1.3)	5.3 (0.6)**	2.3 (0.7)	4.1 (1.3)	4.1 (1.9)

Change in HAQ-DI [mean (Adjusted mean (SE))]									
-0.70 (0.05)	-0.52 (0.05)	-0.5 (0.04)**	-0.3 (0.04)	-0.55 (0.06)**	-0.34 (0.07)	-0.47 (0.03)***	-0.2 (0.03)	-0.39 (0.05)***	-0.05 (0.07)

Change in FACIT-Fatigue [mean (Adjusted mean (SE))]									
9.3 (0.8)	7.0 (0.8)	6.4 (0.7)	5.4 (0.8)	8.6 (0.9)***	4.0 (1.0)	8.0 (0.5)***	3.6 (0.7)	8.8 (1.0)*	4.2 (1.6)

TCZ = tocilizumab

* p<0.05, tocilizumab vs. placebo+MTX/DMARD

** p<0.01, tocilizumab vs. placebo+MTX/DMARD

*** p<0.0001, tocilizumab vs. placebo+MTX/DMARD

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

Laboratory Evaluations

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

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

MTX naïve, Early RA

Study VI, a 2-year study with the planned primary analysis at week 52 evaluated 1162 MTX-naïve adult patients with moderate to severe, active early RA (mean disease duration ≤ 6 months). This study evaluated the efficacy of IV 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 below 2.6) at week 24. A significantly higher proportion of patients in the tocilizumab 8 mg/kg + MTX and tocilizumab monotherapy groups met the primary endpoint compared with MTX alone. The tocilizumab 8 mg/kg + MTX group also showed statistically significant results across the key secondary endpoints. Numerically greater responses compared with MTX alone were observed in the tocilizumab 8 mg/kg monotherapy group in all secondary endpoints, including radiographic endpoints. In this study, ACR/EULAR remission (Boolean and Index) were also analysed as pre-specified exploratory endpoints, with higher responses observed in

the tocilizumab groups. The results from study VI are shown in Table 7.

Table 7: Efficacy results for study VI (WA19926) on MTX-naïve, early RA patients

		TCZ 8 mg/kg + MTX N=290	TCZ 8 mg/kg + placebo N=292	Placebo + MTX N=287
Primary Endpoint				
DAS28 Remission				
Week 24	n (%)	130 (44.8)***	113 (38.7)***	43 (15.0)
Key Secondary Endpoints				
DAS 28 remission				
Week 52	n (%)	142 (49.0)***	115 (39.4)	56 (19.5)
ACR				
Week 24	ACR20, n (%)	216 (74.5)*	205 (70.2)	187 (65.2)
ACR50, n (%)		165 (56.9)**	139 (47.6)	124 (43.2)
ACR70, n (%)		112 (38.6)**	88 (30.1)	73 (25.4)
Week 52	ACR20, n (%)	195 (67.2)*	184 (63.0)	164 (57.1)
ACR50, n (%)		162 (55.9)**	144 (49.3)	117 (40.8)
ACR70, n (%)		125 (43.1)**	105 (36.0)	83 (28.9)
HAQ-DI (adjusted mean change from baseline)				
Week 52		-0.81*	-0.67	-0.64
Radiographic Endpoints (mean change from baseline)				
Week 52	mTSS	0.08***	0.26	1.14
Erosion Score		0.05**	0.15	0.63
JSN		0.03	0.11	0.51
Radiographic Non-Progression n (%) (change from baseline in mTSS of ≤0)		226 (83)‡	226 (82)‡	194 (73)
Exploratory Endpoints				
Week 24: ACR/EULAR Boolean Remission, n (%)		47 (18.4)‡	38 (14.2)	25 (10.0)
ACR/EULAR Index Remission, n (%)		73 (28.5)‡	60 (22.6)	41 (16.4)
Week 52: ACR/EULAR Boolean Remission, n (%)		59 (25.7)‡	43 (18.7)	34 (15.5)
ACR/EULAR Index Remission, n (%)		83 (36.1)‡	69 (30.0)	49 (22.4)

All efficacy comparisons vs Placebo + MTX. ***p≤0.0001; **p<0.001; *p<0.05;

‡p-value < 0.05 vs. Placebo + MTX, but endpoint was exploratory (not included in the hierarchy of statistical testing and has therefore not been controlled for multiplicity)

Monotherapy: Tocilizumab versus Adalimumab

Study WA19924 evaluated 326 patients with RA who were intolerant of MTX or where continued

treatment with MTX was considered inappropriate (including MTX inadequate responders). Patients in the 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 8)

Table 8: Efficacy results for study WA 19924

	ADA + Placebo (IV) N = 162	TCZ + Placebo (SC) N = 163	p-value[a]
Primary Endpoint - Mean Change from baseline at Week 24			
DAS28 (adjusted mean)	**-1.8**	**-3.3**	
Difference in adjusted mean (95% CI)	**-1.5 (-1.8, -1.1)**		**<0.0001**
Secondary Endpoints - Percentage of Responders at Week 24 [b]			
DAS28 < 2.6, n (%)	18 (10.5)	65 (39.9)	<0.0001
DAS28 ≤ 3.2, n (%)	32 (19.8)	84 (51.5)	<0.0001
ACR20 response, n (%)	80 (49.4)	106 (65.0)	0.0038
ACR50 response, n (%)	45 (27.8)	77 (47.2)	0.0002
ACR70 response, n (%)	29 (17.9)	53 (32.5)	0.0023

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

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

Japanese studies in pJIA, sJIA & Castleman's disease

Active Polyarticular-course Juvenile Idiopathic Arthritis (Active pJIA)

Phase III study in Japan

Three doses of tocilizumab 8 mg/kg IV Q4W were administered to 19 patients with active PJIA. The proportion of patients who achieved a 30%, 50%, and 70% improvement in the JIA Core Set[#] at last observation was 94.7%, 94.7%, and 57.9%, respectively, thus demonstrating a marked improvement in underlying disease.

[#]The standard set of criteria proposed by Giannini, et al., for use in therapeutic assessment of patients with juvenile idiopathic arthritis
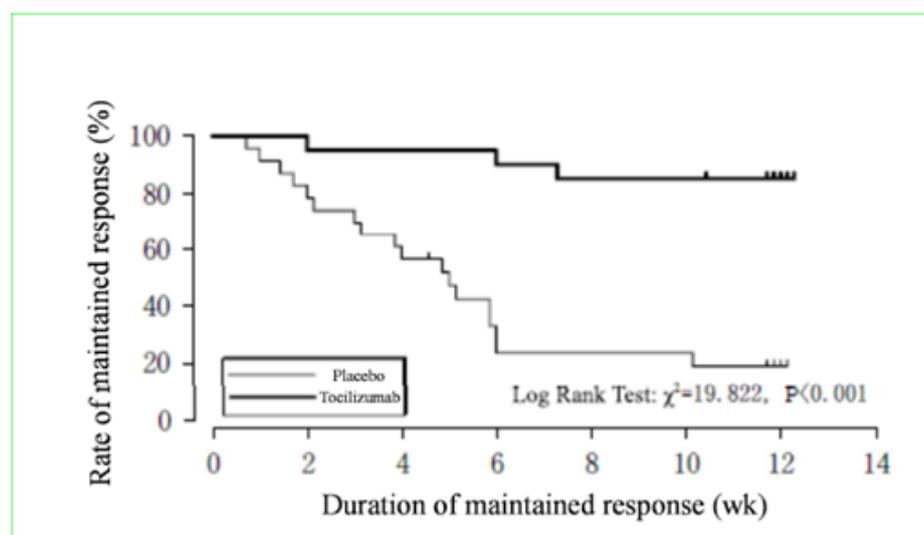
Adverse reactions occurred in 13 out of 19 patients (68.4%),and consisted of upper respiratory tract infection in 5 patients (26.3%), nasopharyngitis in 4 patients (21.1%), diarrhea in 2 patients (10.5%), and tonsillitis, upper respiratory tract inflammation, cheilitis, nausea, stomatitis, eczema, rash, urticaria, blood urine present, and decreased lymphocyte count each in 1 patient (5.3%).

Systemic Juvenile Idiopathic Arthritis (sJIA)

Phase III study in Japan

In this study, 56 patients with SJIA were given 3 doses of tocilizumab 8 mg/kg IV Q2W in an open-label lead-in phase. The 43 patients who achieved both a ≥30% improvement in the JIA core set[#] and an improvement in CRP concentration to <0.5 mg/dL were then selected for efficacy analysis and proceeded to the double-blind comparative phase, where they were randomized to receive six IV Q2W doses of tocilizumab (n=20) or placebo (n=23). The two groups were then compared according to percentage of patients who maintained JIA core set ≥30% improvement and <1.5 mg/dL CRP response, and the duration of maintained response. The study results showed that maintained response rate was significantly higher in the tocilizumab group than in the placebo group, at 80.0% versus 17.4% (P<0.001). Similarly, duration of maintained response was significantly longer in the tocilizumab group than in the placebo group (P<0.001).

Figure 1: Time course of maintained response rate (Kaplan-Meier curve)

Adverse reactions occurred in 53 out of 56 patients (94.6%). The most common adverse reactions were nasopharyngitis in 15 patients (26.8%), increased ALT in 13 patients (23.2%), upper respiratory tract infection in 11 patients (19.6%), increased AST in 8 patients (14.3%), increased blood cholesterol in 8 patients (14.3%), pharyngitis in 7 patients (12.5%), gastroenteritis in 6 patients (10.7%), vomiting in 6 patients (10.7%), and decreased lymphocyte count in 6 patients (10.7%).

Castleman's disease

(1) Phase II study in Japan

Stage I

This study investigated the efficacy of 2, 4, and 8 mg/kg[#] tocilizumab IV Q2W each administered for 3 doses using an intra-patient dose-escalation design in 7 patients with Castleman's disease. The study results showed that at 2 and 4 mg/kg tocilizumab, CRP and other inflammation markers decreased at 1 week post-infusion but increased again at 2 weeks post-infusion. At 8 mg/kg tocilizumab, almost all patients had a sustained decrease in these inflammation markers throughout the treatment period.

#Note: The approved dose of **ACTEMRA** is 8mg/kg (see Dosage and Administration).

Stage II

Tocilizumab 8 mg/kg IV Q2W was administered for a total of 8 doses to 28 patients with Castleman's disease. The study results showed that inflammation markers (CRP, fibrinogen, and erythrocyte sedimentation rate [ESR]), general malaise (assessed using the Visual Analog Scale [VAS]), anemic state (Hb level), and hypoalbuminemia improved significantly for the entire treatment period following the first infusion (Table 9).

Table 9: Time course of efficacy endpoints (Stage II)

Variable	Baseline	From Week 6	From Week 16
CRP (mg/dL)	8.7 ± 5.0	1.2 ± 1.7**	0.9 ± 2.0**
Fibrinogen (mg/dL)	639 ± 188	356 ± 149**	317 ± 138**
ESR (mm/hr)	114 ± 34	63 ± 36	48 ± 40**
Generalised fatigue (0-100mm)	29.9 ± 22.8	17.4 ± 17.2*	17.7 ± 16.5**
Hb (g/dL)	9.2 ± 2.3	11.6 ± 1.9**	12.0 ± 2.1**
Albumin (g/dL)	2.7 ± 0.5	3.6 ± 0.5**	3.7 ± 0.5**

*$P<0.05$,**$P<0.01$, paired t test (n=24-28; mean ± SD)

(2) Extension study

Long-term extended dosing was administered primarily at a dosage of 8 mg/kg Q2W to 33 patients with Castleman's disease who participated in stages 1 and 2 of the study (maximum dosing period: 1568 days; mean dosing period: 1191 days), resulting in a maintained therapeutic effect on inflammation markers and other measured variables. In the 7 patients who responded inadequately to treatment, reduction of the dosing interval to QW yielded an improvement in inflammation markers.

Adverse reactions occurred in 33 out of 35 patients (94.3%). The most common adverse reactions were nasopharyngitis in 28 patients (80.0%), rash in 11 patients (31.4%), pruritus in 10 patients (28.6%), decreased neutrophil count in 9 patients (25.7%), oropharyngeal pain in 8 patients (22.9%), diarrhea in 7 patients (20.0%), back pain in 7 patients (20.0%), malaise in 7 patients (20.0%), abnormal blood thrombin in 7 patients (20.0%), and increased blood triglycerides in 7 patients (20.0%).

3.2 Pharmacokinetics Properties

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

Rheumatoid Arthritis

The pharmacokinetics in healthy subjects and RA patients suggest that PK is similar between the

two populations. The table below shows model predicted secondary PK parameters at each of the four approved dose regimens. The population PK (popPK) model was developed from an analysis dataset composed of an IV dataset of 1793 patients from studies WA17822, WA17824, WA18062 and WA18063 and IV and SC dataset of 1759 patients from studies WA22762 and NA25220. Cmean is included in the table since for dosing regimens with different inter-dose interval, the mean concentration over the dosing period characterizes the comparative exposure better than AUCτ.

Table 10: Predicted mean ± SD PK parameters at steady-state after IV and SC dosing in RA

	IV		SC	
TCZ PK Parameter	**4 mg/kg Q4W**	**8 mg/kg Q4W**	**162 mg Q2W**	**162 mg QW**
C_{max} (mcg/mL)	83.8 ± 23.1	182 ± 50.4	13.2 ± 8.8	49.8 ± 21.0
C_{trough} (mcg/mL)	0.5 ± 1.5	15.9 ± 13.1	5.7 ± 6.8	43.0 ± 19.8
C_{mean} (mcg/mL)	17.8 ± 6.1	56.6 ± 19.3	10.2 ± 8.0	47.4 ± 20.5
Accumulation C_{max}	1.01	1.09	2.12	5.27
Accumulation C_{trough}	2.62	2.47	6.02	6.30
Accumulation C_{mean} or AUC_{τ} *	1.09	1.32	2.67	6.32

*τ = 4 weeks for IV regimens, 2 week or 1 week for the two SC regimens, respectively

At high serum concentrations, when total clearance of tocilizumab is dominated by linear clearance, a terminal half-life of approximately 21.5 days was derived from the population parameter estimates.

While after IV administration maximum concentration (C_{max}) increased dose-proportionally between doses of 4 and 8 mg/kg IV every 4 weeks, a greater than dose-proportional increase was observed in the average concentration (C_{mean}) and trough concentration (C_{trough}). At steady-state, C_{mean} and C_{trough} were 3.2 and 32-fold higher at 8 mg/kg as compared to 4 mg/kg, respectively. Exposures after the 162 mg SC QW regimen were greater by 4.6 (C_{mean}) to 7.5-fold (C_{trough}) compared to the 162 SC Q2W regimen.

The accumulation ratios for AUC and C_{max} after multiple doses of 4 and 8 mg/kg Q4W are low, while the accumulation ratios are higher for C_{trough} (2.62 and 2.47). Accumulation ratios after multiple doses of either SC regimen were higher than after IV regimen with the highest ratios for C_{trough} (6.02 and 6.30). The higher accumulation for C_{trough} was expected based on the nonlinear clearance contribution at lower concentrations.

For C_{max}, more than 90% of the steady-state was reached after the 1st IV infusion, and after the 12th SC and the 5th SC injection in QW and Q2W regimens respectively. For AUC_{τ} and C_{mean}, 90% of the steady-state was reached after the 1st and 3rd infusion for the 4 mg/kg and 8 mg/kg IV, respectively, and after the 6th and 12th injections for the 162 mg SC Q2W and QW regimens respectively. For C_{trough}, approximately 90% of the steady-state was reached after the 4th IV infusion, the 6th and 12th injections for the respective SC regimens.

Population PK analysis identified body weight as a significant covariate impacting pharmacokinetics of tocilizumab. When given IV on a mg/kg basis, individuals with body weight ≥ 100 kg are predicted to have mean steady-state exposures higher than mean values for the patient population. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended in patients [3] 100 kg (*see section 2.2 Dosage and Administration)*. Due to the flat dosing employed for SC administration of tocilizumab, no modifications are necessary by this dosing route.

Pharmacokinetics in patients with Active polyarticular-course juvenile idiopathic arthritis (active

pJIA)

Multiple doses

Three doses of Tocilizumab 8 mg/kg 1-hour IV Q4W were administered to 19 patients with active pJIA (aged: 3-19 years; median age: 12 years). A comparison of serum Tocilizumab pharmacokinetic parameters after the first infusion is shown in Table 11. The elimination rate of serum tocilizumab was high in some patients in the group aged <7 years.

Table 11: Pharmacokinetic parameters of tocilizumab after multiple IV infusions in patients with active pJIA

Age	C_{1hr} (µg/mL)	AUC_{last} (µg *hr/mL)	$t_{1/2}$ (hr)	CL_{total} (mL/hr/kg)	MRT (hr)	V_{dss} (mL/kg)
3 to < 7	107.8 ± 15.0	12970 ± 2511	NA	NA	NA	NA
7 to <15	158.6 ± 34.4	20878 ± 5328	99 ± 12	0.3 ± 0.0	150 ± 9	48.0 ± 7.0
> 15	158.1 ± 36.2	25954 ± 6157	143 ± 43	0.3 ± 0.1	200 ± 49	60.5 ± 12.2
All	145.0 ± 37.5	25275 ± 6722	123 ± 41	0.3 ± 0.1	178 ± 46	58.3 ± 13.9

(mean ± SD, NA: not calculated) (3 to <7 years: C_{1hr} and AUC_{last} n=5, 7 to <15 years: C_{1hr} and AUC_{last}: n=7, other parameters: n=4, ≥15: n=7)

Pharmacokinetics in patients with systemic juvenile idiopathic arthritis (sJIA)

Multiple doses

Three multiple doses of Tocilizumab 8 mg/kg 1-hour IV Q2W were administered to patients with SJIA (age range: 2-19 years; median age: 8 years), and then a further 6 doses were administered to those who responded to treatment ("responders"), for a total of 9 doses given over an 18-week treatment period.

The serum tocilizumab Pharmacokinetic parameters after the first and third infusions are shown in Table 12. The elimination rate of serum tocilizumab was high in some patients in the group aged <7 years.

The time course of serum tocilizumab concentration suggests that steady state was reached between 8 and 14 weeks after the first infusion. The serum tocilizumab concentration immediately before infusion 18 weeks after the first infusion was 57.4 µg/mL (n=13).

The elimination rate of Serum tocilizumab levels tended to be higher in patients who were younger or who had a lower body weight or, height.

Table 12: Pharmacokinetic parameters of tocilizumab after multiple IV infusions in patients with sJIA

Age	No. of doses	C_{1hr} (µg/mL)	AUC_{last} (µg *hr/mL)	$t_{1/2}$ (hr)	CL_{total} (mL/hr/kg)	MRT (hr)	V_{dss} (mL/kg)
2 to < 7	1	142.8 ± 31.6	17677 ± 5193	NA	NA	NA	NA
	3	171. 7 ± 51.2	23706 ± 9704	100 ± 38	0.3 ± 0.1	155 ± 60	45.4 ± 7.6
7 to < 15	1	176.7 ± 48.5	24701 ±7611	NA	NA	NA	NA
	3	239.8 ± 70.2	35333 ± 11668	127 ± 26	0.2 ± 0.2	188 ± 49	43.0 ± 17.5

| > 15 | 1 | 166.0 ± 31.8 | 23653 ± 3571 | NA | NA | NA | NA |
| | 3 | 214.0 ± 40.0 | 33336 ± 8115 | 139 ± 30 | 0.2 ± 0.0 | 249 ± 21 | 43.6 ± 11.2 |

(Mean ± SD, NA: not calculated) (2 to <7 years: n=19-23, 7 to <15 years: n=25-28, ≥15 years: n=4-5)

Pharmacokinetics in patients with Castleman's disease

Multiple doses

Eight multiple doses of Tocilizumab 8 mg/kg 1-hour IV Q2W were   administered to 28 patients with Castleman's disease. The serum tocilizumab concentration increased from after the first infusion,and was 36.6 ± 17.5 µg/mL at the pre-8th infusion time point. Both $t_{1/2}$ and MRT were extended up to the sixth infusion but remained almost constant from the sixth infusion onwards (Table 13).

Table 13: Pharmacokinetic parameters of tocilizumab after multiple IV infusions in patients Castleman's disease

Dose (mg/kg)	No. of doses	C_{max} (µg/mL)	AUC_{last} (µg *hr/mL)	$t_{1/2}$ (hr)	CL_{total} (mL/hr/kg)	MRT (hr)	V_{d25} (mL/kg
8	1	112.9 ± 24.7	13092 ± 3254	99.7 ± 17.1	0.6 ± 0.2	145 ± 26.8	80.1 ± 15.0
	8	192.3 ± 38.7	28423 ± 7410	139 ± 37.4	0.2 ± 0.1	205 ± 54.2	46.8 ± 8.8

(No. of patients: =26-28; mean ± SD)

3.2.1 Absorption

No text.

3.2.2 Distribution

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

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

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

3.2.3 Metabolism

No text.

3.2.4 Elimination

The total clearance of tocilizumab was concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 12.5 mL/h in RA patients, 5.8 mL/h in paediatric patients with polyarticular juvenile idiopathic arthritis and 5.7 mL/h in paediatric patients with

systemic juvenile idiopathic arthritis. The concentration-dependent nonlinear clearance plays a major role at low tocilizumab concentrations. Once the nonlinear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance. Due to dependence of total clearance on tocilizumab serum concentrations, t1/2 of tocilizumab is also concentration dependent and can only be calculated at a given serum concentration level.

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

3.2.5. Pharmacokinetics in Special Populations

Hepatic Impairment

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

Renal impairment:

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

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

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

Other special populations

Population pharmacokinetic analyses in adult RA patients showed that age, sex and race did not affect pharmacokinetics of tocilizumab. No dose adjustment is necessary for these demographic factors.

3.3 Nonclinical Safety

3.3.1 Carcinogenicity

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

3.3.2 Genotoxicity

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

3.3.3 Impairment of Fertility

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

3.3.4 Reproductive Toxicity

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

3.3.5 Other

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

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

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

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

4. Pharmaceutical Particulars

4.1 Storage

Intravenous tocilizumab

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

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

For prepared infusion solution: The prepared infusion solution of tocilizumab is physically and chemically stable in 0.9% w/v sodium chloride solution at 30ºC for 24 hours.

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

4.2 Special Instructions for Use, Handling and Disposal

Intravenous tocilizumab

Parenteral medications should be inspected visually for particulate matter or discoloration prior to

administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles must be infused.

Use a sterile needle and syringe to prepare Tocilizumab.

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

4.3 Shelf Life

Unopened vial: 30 months when stored at recommended storage conditions.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater, and disposal through household waste should be avoided. Use established 'collection systems' if available in your location.

4.4 Pack Sizes (vials for IV infusion use only)

Presentations	Pack sizes
Vials 80 mg/4 ml	1
Vials 200 mg/10 ml	1
Vials 400 mg/20 ml	1

Keep out of reach of children

4.5 Incompatibilities

No text

5. Description

Tocilizumab is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass with a typical H2L2 polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. **ACTEMRA** has a molecular weight of approximately 148 kDa. The antibody is produced in mammalian (Chinese hamster ovary) cells.

ACTEMRA (tocilizumab) injection is a clear to opalescent, colourless to pale yellow liquid, supplied in preservative-free, non-pyrogenic single-use vials, supplied in 10 mL and 20 mL vials containing 4 mL, 10 mL or 20 mL of Tocilizumab (20 mg/mL).

Excipients: Sucrose, Polysorbate 80, Disodium phosphate dodecahydrate, Sodium dihydrogen phosphate dihydrate and Water for injections

6. Patient Counseling Information

Patient Counseling

Advise patients and parents or guardians of minors with PJIA or SJIA of the potential benefits and risks of **ACTEMRA**.

Infections

- Inform patients that **ACTEMRA** may lower their resistance to infections. Instruct the patient of the importance of contacting their doctor immediately when symptoms suggesting infection appear in order to assure rapid evaluation and appropriate treatment.

Gastrointestinal Perforation

- Inform patients that some patients who have been treated with **ACTEMRA** have had serious side effects in the stomach and intestines. Instruct the patient of the importance of contacting their doctor immediately when symptoms of severe, persistent abdominal pain appear to assure rapid evaluation and appropriate treatment.

Hypersensitivity and Serious Allergic Reactions

- Assess patient suitability for home use for subcutaneous injection. Inform patients that some patients who have been treated with **ACTEMRA** have developed serious allergic reactions, including anaphylaxis. Advise patients to seek immediate medical attention if they experience any symptom of serious allergic reactions.

7. Details of Manufacturer

Manufactured by: F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, CH-4070, Basel, Switzerland at Chugai Pharma Manufacturing Co., Ltd., 16-3, Kiyohara Kogyodanchi, Utsunomiya-City, Tochigi 321-3231, Japan

Imported by:

Roche Products (India) Pvt. Ltd.,

C/O. Parekh Integrated Services Pvt. Ltd, Gala No. A1, First Floor, Warehouse no. 6, BGR Logistics Park, NH-3, Zone 5, Bhiwandi, Maharashtra (India) – 421302

Distributed and Marketed by:

Cipla

Cipla Ltd., Cipla House, Peninsula Business Park,

Ganpatrao Kadam Marg, Lower Parel, Mumbai 400 013, India

8. Details of Permission or Licence Number with Date

Import permission No.: Import-930/08 dated 29 Aug 2008.

9. Date of Revision

Current at February 2021, Version 13.0