Actemra®

Tocilizumab

Composition

Active substance

Tocilizumab.

Excipients

Concentrate for solution for infusion

Sucrose, polysorbate 80, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, water for injection.

Injection solution for subcutaneous use

L-histidine, L-histidine hydrochloride monohydrate, L-arginine, L-arginine hydrochloride, L-methionine, polysorbate 80, water for injection.

Pharmaceutical form and quantity of active substance per unit

Concentrate for solution for infusion.
- Each 4 ml vial contains 80 mg tocilizumab (20 mg/ml).
- Each 10 ml vial contains 200 mg tocilizumab (20 mg/ml).
- Each 20 ml vial contains 400 mg tocilizumab (20 mg/ml).

Injection solution for subcutaneous use:

Each 0.9 ml prefilled syringe contains 162 mg tocilizumab (180 mg/ml).

Indications and potential uses

Rheumatoid arthritis (RA) [i.v. and s.c. formulation]

Actemra is indicated for the treatment of adult patients with active moderate to severe rheumatoid arthritis who have failed to respond adequately, or have developed adverse reactions, to treatment with disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX). Actemra may be used alone or alternatively in combination with conventional synthetic DMARDs (csDMARDs), including MTX. Combination therapy with MTX has been shown to slow progression of structural damage and improve physical function.

Rheumatoid arthritis (RA) [i.v. formulation]

In treatment-naïve patients with moderate to severe rheumatoid arthritis, improved control of symptoms and signs of rheumatoid arthritis and slowing of progression of

structural damage were seen with Actemra, both in combination therapy with methotrexate and in monotherapy (see Properties and effects).

Polyarticular juvenile idiopathic arthritis (PJIA) [i.v. formulation only]

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

Systemic juvenile idiopathic arthritis (SJIA) [i.v. formulation only]

Treatment of children and adolescents aged 2 years and above with systemic juvenile idiopathic arthritis who have failed to respond adequately to prior therapy with non-steroidal anti-inflammatory drugs and steroids. Actemra was administered in the clinical studies in combination with corticosteroids and DMARDs, including methotrexate. There is limited experience on the benefit of Actemra monotherapy without corticosteroids.

Dosage and administration

General information

Intravenous (i.v.) formulation

The i.v. formulation of Actemra is not intended for subcutaneous administration.
Treatment with Actemra must be initiated and conducted under the supervision of a physician experienced in the management of patients with rheumatoid arthritis (see *Warnings and precautions*).
Actemra should be diluted under aseptic conditions by a qualified healthcare professional in sterile 0.9% (w/v) sodium chloride solution (see *Additional information, Instructions for handling*).

The recommended duration of the i.v. infusion is one hour.

Subcutaneous (s.c.) formulation

The s.c. formulation of Actemra is not intended for intravenous administration.

The s.c. formulation of Actemra is administered using a single-use prefilled syringe with a needle safety device. The first injection should be performed under the supervision of an appropriately trained healthcare professional. Patients should receive the patient card. Patients may self-inject Actemra only if the physician considers this appropriate and the patient agrees to the necessary medical follow-up and has been trained in proper injection technique. The recommended injection sites (abdomen, thigh and upper arm) should be changed each time and injections should never be given into moles, scars or areas of tender, injured, reddened, indurated or non-intact skin. Patients switching from i.v. tocilizumab treatment to s.c. administration should give themselves the first s.c. dose at the time of the next scheduled i.v. dose under the supervision of an appropriately trained healthcare professional.

The patient’s (or parents’ or caregiver’s) suitability for s.c. home use must be assessed. Patients (or parents or caregivers) must be instructed to inform a healthcare professional

before administering the next dose if they experience (or notice in the patient) symptoms of an allergic reaction. Patients should seek immediate medical attention if they develop symptoms of a serious allergic reaction (*see Warnings and precautions and Undesirable effects*).

To ensure the traceability of biological medicinal products, it is recommended that the trade name and batch number be documented with every treatment.

Adults (rheumatoid arthritis) [i.v. and s.c. formulation]

Adults with RA may be given Actemra as an i.v. infusion or s.c. injection.

Intravenous dosage regimen

The recommended dose of Actemra is 8 mg/kg body weight (BW) administered once every 4 weeks by intravenous infusion over 1 hour.
Patients weighing more than 100 kilograms (kg) should not receive single doses exceeding 800 mg.

Subcutaneous dosage regimen

The recommended dose of Actemra in adult patients is 162 mg, administered once weekly by subcutaneous injection. In patients weighing <60 kg and comedicated with methotrexate, the initial dosage is 162 mg every 2 weeks (see also study SC-II under Properties and effects below). If the response is inadequate, the dose may be increased to 162 mg once weekly.

In patients with a clinical response to once-weekly dosing with 162 mg Actemra in combination with methotrexate, a dose reduction to 162 mg every two weeks should be considered after 12 weeks. Dose reduction is not recommended in monotherapy patients on once-weekly dosing.

In patients responding inadequately to weekly subcutaneous administration of 162 mg and weighing >100 kg, a switch to intravenous Actemra 800 mg every 4 weeks should be considered.

Children and adolescents: 2–-18 years (polyarticular juvenile idiopathic arthritis [PJIA]) [i.v. formulation]

Patients with PJIA are given Actemra as an i.v. infusion. A change in dose should only be based on a corresponding change in the patient's body weight over time. Tocilizumab can be used alone or in combination with MTX.

The recommended dose is 8 mg/kg body weight (BW) once every 4 weeks (intravenous infusion over 1 hour).

The dose may be increased to 10 mg/kg in patients below 30 kg who have not responded to the recommended standard dose of 8 mg/kg after 8 weeks.

Only limited data are available on patients under 5 years of age.

Children and adolescents: 2–18 years (systemic juvenile idiopathic arthritis [SJIA]) [i.v. formulation]

Patients with SJIA are given Actemra as an i.v. infusion. A change in dose should only be based on a consistent change in the patient's body weight over time. Tocilizumab can be used alone or in combination with MTX.

The recommended dose is:

- 12 mg/kg in patients weighing less than 30 kg
- 8 mg/kg in patients weighing ≥30 kg

once every two weeks (intravenous infusion over one hour).

Special dosage instructions

Use in children and adolescents

The safety and efficacy of Actemra in PJIA patients under 2 years old have not been evaluated. The safety and efficacy of Actemra i.v. in SJIA patients under 2 years old have not been evaluated. Actemra has not been studied in children and adolescents with joint diseases other than PJIA or SJIA.

Use in elderly patients (≥65 years)

No dose adjustment is necessary.

Patients with renal impairment

No dose adjustment is required in patients with mild or moderate renal impairment. Actemra has not been studied in patients with moderate to severe renal impairment.

Patients with hepatic impairment

Actemra has not been studied in patients with hepatic impairment.

Patients with elevated transaminase levels

Laboratory changes requiring dose adjustment are frequently seen during treatment with Actemra:

In patients with elevated transaminases (ALT or AST greater than 1.5 × upper limit of normal [ULN]), Actemra therapy must only be initiated with caution. Actemra should not be administered to patients with ALT or AST >5 × ULN.

In RA, PJIA and SJIA, ALT/AST levels should be monitored every 4 to 8 weeks in the first 6 months of treatment and every 12 weeks thereafter.

If the ALT or AST levels exceed 1-3 × ULN, it is recommended that the dose of DMARDs coadministered with Actemra, such as MTX, leflunomide or sulfasalazine, be adjusted.

Patients receiving treatment with intravenous Actemra

If elevation >1-3 × ULN persists despite these measures, the dose of Actemra must be adjusted in order to normalise the ALT/AST levels (reduce Actemra dose to 4 mg/kg or interrupt treatment until ALT/AST levels have returned to normal, then reintroduce treatment at 4 mg/kg or 8 mg/kg when clinically feasible).

Patients receiving treatment with subcutaneous Actemra

For patients with persistently elevated levels in this range the injection schedule should be reduced to once every two weeks or treatment with tocilizumab should be suspended until ALT/AST levels have returned to normal. Treatment can be reintroduced with injections every week or every two weeks when clinically feasible.

If ALT/AST levels >3-5 × ULN are confirmed on repeat testing, Actemra therapy should be suspended. Actemra treatment can be reintroduced at a dosage of 4 or 8 mg/kg BW once the patient's transaminases return to levels <3 × ULN.

Patients with reduced neutrophil or platelet counts

RA

Treatment is not recommended or Actemra should be discontinued in patients with an absolute neutrophil count of $<0.5 \times 10^9$/L or a platelet count of $<50 \times 10^9$/L.

Neutrophil and platelet counts should be checked 4-8 weeks after starting treatment, then as often as considered necessary by the attending physician.

Neutrophils

If the neutrophil count falls below 1×10^9/L but continues to exceed 0.5×10^9/L, treatment should be suspended.

Dose adjustment for i.v. Actemra

As soon as the neutrophil count returns to above 1×10^9/L, treatment can be resumed at the reduced dosage of 4 mg/kg BW. Return to the dose of 8 mg/kg BW is recommended when clinically feasible.

Dose adjustment for s.c. Actemra

If the neutrophil count falls below 1×10^9/L but continues to exceed 0.5×10^9/L, treatment should be suspended.

As soon as the neutrophil count returns to above 1×10^9/L, treatment can be resumed with an alternate-week injection schedule, which can be increased to once weekly when clinically feasible.

Platelets

If the platelet count falls below 100×10^9/L but continues to exceed 50×10^9/L, treatment should be suspended.

Dose adjustment for i.v. Actemra

As soon as the platelet count returns to above 100×10^9/L, treatment can be resumed at the reduced dosage of 4 mg/kg BW. Return to the dose of 8 mg/kg BW is recommended when clinically feasible.

Dose adjustment for s.c. Actemra

As soon as the platelet count returns to >100 × 10^9/L, treatment can be resumed with an alternate-week injection schedule, which can be increased to once weekly when clinically feasible.

PJIA/SJIA

Treatment is not recommended or Actemra should be discontinued in patients with an absolute neutrophil count of <0.5 × 10^9/L or a platelet count of <50 × 10^9/L.

The decision to discontinue Actemra in patients with PJIA/SJIA because of laboratory abnormalities should be based on a medical examination of the individual patient.

In patients with PJIA or SJIA, neutrophils should be checked at the time of the second administration, then as often as considered necessary by the attending physician.

Neutrophils

Dose adjustment for i.v. Actemra

If the neutrophil count falls below 1 × 10^9/L but continues to exceed 0.5 × 10^9/L, treatment should be suspended. As soon as the neutrophil count returns to above 1 × 10^9/L, treatment can be resumed.

Platelets

If the platelet count falls below 100 × 10^9/L but continues to exceed 50 × 10^9/L, treatment should be suspended.

The dose of coadministered MTX may also require adjustment.

Dose adjustment for i.v. Actemra

As soon as the platelet count returns to above 100 × 10^9/L, treatment can be resumed.

Contraindications

Actemra is contraindicated in known hypersensitivity to the active substance or any of the constituent excipients.

Combination with TNF-alfa inhibitors simultaneously or up to 1 month after treatment with anti-TNF antibodies.

Warnings and precautions

Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including tocilizumab.

Actemra should not be administered to patients with active infection. Patients with recurrent infections or with underlying diseases predisposing to infection (e.g. diverticulitis, diabetes and interstitial lung disease) should be treated with caution.

Increased vigilance for timely detection of serious infection is recommended for patients treated with immunosuppressants such as Actemra for moderate to severe RA, PJIA or SJIA, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants. When investigating a patient for suspected infection, it is important to bear in mind the impact of IL 6 inhibition on C reactive protein (CRP) and neutrophils. Inhibition of IL 6 may weaken the response to infection as manifested by the CRP concentration and neutrophil count. Patients (including younger children who may be less able to communicate their symptoms) and parents/guardians of minors should be instructed to contact a healthcare professional immediately when any symptoms suggesting infection appear, in order to ensure rapid evaluation and appropriate treatment.

Immunosuppression

Actemra therapy may impair the humoral immune response.

Complications of diverticulitis

Cases of diverticular perforation have been reported as a complication of diverticulitis in adults treated with Actemra. Tocilizumab should be used with caution in patients with a history of intestinal ulceration or diverticulitis. Patients developing acute abdominal pain should be evaluated promptly for early identification of gastrointestinal perforation.

Tuberculosis

As recommended for other biological treatments, all patients should be screened for latent tuberculosis infection prior to initiating Actemra therapy. Patients with latent tuberculosis should receive standard antimycobacterial therapy before starting Actemra.

Hypersensitivity reactions

In the post-marketing setting, events of serious hypersensitivity and anaphylaxis, including in some cases with a fatal outcome, have occurred in patients treated with a range of doses of Actemra, with or without concomitant arthritis therapies, premedication or a previous hypersensitivity reaction. These events have occurred as early as the first infusion of Actemra.

Anaphylactic reactions may present in particular with circulatory symptoms, bronchial obstruction, angioedema (with possible airway involvement) and abdominal or cutaneous symptoms (urticaria, erythema, pruritus). Before receiving Actemra, patients should be asked whether they have experienced such symptoms or other adverse reactions to previous infusions and, if so, how they tolerated them. It should also be ensured that appropriate facilities and staff are available for emergency treatment of anaphylactic reactions. Patients must be closely monitored during and after the infusion. In the event of an anaphylactic or other serious hypersensitivity reaction, tocilizumab administration must be immediately and permanently stopped, and appropriate treatment initiated (positioning, oxygen, volume replacement plus intramuscular adrenaline [epinephrine], generally in 0.3 mg doses, followed by further drugs such as antihistamines and glucocorticosteroids).

If subcutaneous use of the product without medical supervision is considered, patients should be informed about possible symptoms of a hypersensitivity reaction before starting treatment. For this purpose Roche provides various training and information brochures for professionals and patients (patient ID card, patient brochure and doctor's brochure). In the event of hypersensitivity reactions, patients must inform their doctor immediately and, if necessary, seek emergency treatment.

Hepatotoxicity

An increase in transaminases may occur during Actemra therapy, in particular during coadministration with MTX. For this reason, caution is essential when administering Actemra to patients with active hepatic disease or hepatic impairment.

A mild to moderate, transient and sometimes recurrent increase was observed in transaminases (ALT or AST) during Actemra therapy (see *Undesirable effects*). An increased frequency of such elevations was observed when drugs known to be hepatotoxic (e.g. methotrexate [MTX]) were used in combination with tocilizumab.

Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, has been observed with Actemra (see Undesirable effects). Serious hepatic injury occurred from 2 weeks to more than 5 years after initiation of Actemra. Cases of liver failure requiring liver transplantation have been reported.

For dose modification recommendations, including Actemra withdrawal, for patients with elevated transaminase levels, see Dosage and administration, Special dosage instructions.

Reactivation of hepatitis B

Rare cases of hepatitis B reactivation have been observed with the use of immunosuppressants in rheumatoid arthritis. Currently available data do not definitely exclude the possibility of hepatitis reactivation in patients on Actemra therapy.

Preventive vaccinations

Neither live nor attenuated vaccines should be coadministered with Actemra as no clinical safety data are available.

No data are available on the secondary transmission of infection from persons given live vaccine to patients treated with Actemra. Similarly, no conclusive data are available on viraemia or the effects on vaccine reactions after active vaccination. Antibody response to preventive vaccination may be impaired.

In a clinical trial in 91 patients, immune response to 12 pneumococcal antigens studied after vaccination with Pneumovax 23 was found to be reduced on treatment with Actemra and methotrexate compared to a control group receiving methotrexate alone. The proportion of patients with an increase in antibody titres to tetanus toxoid was approximately 40% in both groups, and is thus lower than the proportion of responders observed following vaccination in healthy vaccinated subjects. Vaccination with pneumococcal and tetanus antigens should therefore be carried out before starting treatment with Actemra.

It is recommended that all patients, particularly paediatric or elderly patients, if possible be brought up to date with all vaccinations in accordance with current vaccination guidelines before starting treatment with Actemra. The interval between live vaccinations and initiation of Actemra therapy should be consistent with current vaccination guidelines regarding immunosuppressive agents.

Influence on serological diagnosis of infections

A potential impact of Actemra therapy on the serological diagnosis of specific infections cannot be excluded as no studies have been undertaken on this question.

Effects on full blood count

Cases of decreased neutrophil and platelet counts have been observed on treatment with Actemra (see *Undesirable Effects*).

In patients with a low neutrophil or platelet count (i.e. absolute counts below 2×10^9/L and below 100×10^9/L, respectively), caution must be observed when initiating Actemra therapy.

For dose modification recommendations for patients with reduced neutrophil or platelet counts, see Dosage and administration, Special dosage instructions.

Malignancy

Patients with rheumatoid arthritis are at increased risk of malignancy. Clinical data are insufficient to estimate the possible incidence of malignant disease after Actemra administration, although the available data do not suggest an increased risk of malignancy.Results of long-term safety studies are not yet available.

Cardiovascular risks

Patients with rheumatoid arthritis are at increased risk of cardiovascular disease. Close monitoring (ECG, blood pressure) is therefore required, in particular in patients with risk factors such as hypertension, dyslipidaemia and diabetes.

Activation of the complement system

Although activation of the complement system during treatment cannot be excluded, the preclinical and clinical data currently available provide no evidence to this effect.

Lipid parameters

Elevations in lipid parameters such as total cholesterol, triglycerides and/or low density lipoprotein (LDL) have been observed (see *Undesirable Effects*).
In patients treated with Actemra, lipid parameters should be measured 4 to 8 weeks after the start of Actemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

Demyelinating disorders
Physicians should be vigilant for symptoms potentially indicative of new-onset demyelinating central nervous system (CNS) disorders. The potential for CNS demyelination with tocilizumab is currently unknown.

Macrophage activation syndrome (MAS)
MAS is a serious, life-threatening condition that may develop in patients with SJIA. Actemra has not been investigated in clinical study patients during an MAS episode.

Interactions

The pharmacokinetics of tocilizumab in RA patients are unaffected by coadministration of other antirheumatic agents (MTX, chloroquine and its derivatives [antimalarials], immunosuppressants [azathioprine, leflunomide], corticosteroids [prednisone and derivatives], folic acid and its derivatives, non-steroidal anti-inflammatory drugs [diclofenac, ibuprofen, naproxen, meloxicam, COX-2 inhibitors (celecoxib)], and analgesics [paracetamol, tramadol, codeine and derivatives]). Coadministration of a single dose of 10 mg/kg Actemra with 10–25 mg MTX once weekly had no clinically significant effect on MTX exposure.

Actemra has not been studied in combination with other biological agents such as tumour necrosis factor (TNF) inhibitors.

The expression of hepatic CYP450 enzymes is suppressed by cytokines, such as IL-6, that stimulate chronic inflammation. Thus, CYP450 expression may be altered on initiation of cytokine inhibition with tocilizumab.

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

Levels of simvastatin, which is metabolised by CYP3A4, were reduced by 57% one week after a single dose of tocilizumab. Therefore, patients taking medicinal products whose dose is individually adjusted and which are metabolised by CYP450 3A4, 1A2 or 2C9 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin or benzodiazepines) should be monitored when starting or stopping therapy with tocilizumab, and the dose of these agents adjusted as required. Given its long elimination half-life, the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

Pregnancy and lactation

Pregnancy
Insufficient data are available to support use of Actemra in pregnant women. A study in monkeys produced no evidence of teratogenic potential, but showed a greater number of spontaneous abortions/embryo-foetal deaths at high dose. The potential risk to humans is unknown.
Actemra must not be administered during pregnancy unless the prescribing physician considers its use clearly necessary.

Lactation

Excretion of a tocilizumab surrogate antibody in milk has been demonstrated in mice (see *Preclinical data*). It is not known whether Actemra is excreted in breast milk; nursing mothers should therefore discontinue breastfeeding if use of the product is considered essential.

Effects on ability to drive and use machines

No studies have been performed on the effects on the ability to drive and use machines. However, there is no evidence that treatment with Actemra impairs the ability to drive or use machines.

Undesirable effects

The safety profile in this section comes from 4510 patients treated with tocilizumab in clinical trials; the majority of these patients were participating in RA studies (n=4009), while the remaining data come from PJIA and SJIA studies. The safety profile of tocilizumab across these indications remains similar and undifferentiated.

The adverse drug reactions (ADRs) are listed by MedDRA system organ class and according to their 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), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), not known (frequency cannot be determined from post-marketing experience).

Adverse reactions, clinical trials and post-marketing experience

Immune system disorders

Common: hypersensitivity reactions.
Uncommon: anaphylaxis (sometimes fatal*) (see *Contraindications* and *Warnings and precautions).*
*post-marketing reports

Infections and infestations
Very common: upper airways infections (12.4%).
Common: orolabial herpes simplex, shingles.

There have been isolated reports of opportunistic infections (including serious and sometimes fatal cases).

Blood and lymphatic system disorders
Common: leukopenia, neutropenia, hypofibrinogenaemia (observed in the post-marketing setting).
Uncommon: thrombocytopenia.

Endocrine disorders
Uncommon: hypothyroidism.

Metabolism and nutrition disorders
Common: hypercholesterolaemia.

Uncommon: hypertriglyceridaemia.

Nervous system disorders
Common: headache, dizziness.

Eye disorders
Common: conjunctivitis.

Vascular disorders
Common: hypertension.

Respiratory, thoracic and mediastinal disorders
Common: cough, dyspnoea.
Frequency not known: There have been post-marketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Gastrointestinal disorders
Common: stomatitis, gastritis, abdominal pain.
Uncommon: diverticulitis, gastrointestinal perforation, gastric ulcer.

Hepatobiliary disorders
Common: increase in transaminases.
Rare: drug-induced liver injury, hepatitis, jaundice.
Very rare: hepatic failure.
Uncommon: increase in total bilirubin.

Skin and subcutaneous tissue disorders
Common: cellulitis, rash, pruritus, urticaria.

Rare: Stevens-Johnson syndrome (SJS) (identified in the post-marketing setting).

Renal and urinary disorders
Uncommon: nephrolithiasis.
General disorders and administration site conditions
Very common: injection site reaction (28.8%).
Common: peripheral oedema.

Investigations
Common: weight gain.

Description of selected adverse drug reactions from clinical trials:

Rheumatoid arthritis
Patients receiving treatment with intravenous Actemra
Of 4009 patients with RA in clinical studies, 3577 received treatment for at least 6 months, 3296 for at least one year, 2806 for at least 2 years and 1222 for 3 years.
In study WA25204, elevations in ALT or AST to >3 × ULN occurred in 5.3% and 2.2%, respectively, of the 1538 patients with moderate to severe RA during treatment with Actemra. One serious event of drug-induced hepatitis with hyperbilirubinaemia was reported in association with Actemra treatment (see Warnings and precautions).

Patients receiving treatment with subcutaneous Actemra
The safety of subcutaneous Actemra in RA patients was investigated in study SC I (WA22762). This study compared the efficacy and safety of tocilizumab 162 mg administered once weekly with 8 mg/kg i.v. in 1262 adult RA patients. All study patients received background therapy with one or more non-biological DMARDs. The safety and immunogenicity observed with tocilizumab administered s.c. matched the known safety profile of i.v. tocilizumab. No new or unexpected adverse drug reactions were observed. A higher frequency of injection site reactions was observed in the s.c. tocilizumab treatment arms than with s.c. injections of a placebo in the i.v. treatment arms (see Clinical efficacy).
The adverse effects most frequently reported (in ≥5% of patients receiving Actemra alone or combined with standard DMARDs) were upper airways infections, nasopharyngitis, headache, hypertension and ALT elevation.

Immunogenicity

i.v. administration: Antibodies against tocilizumab have been observed in 1.6% of cases and neutralising antibodies in 1.1%. The latter had no effect on efficacy.

A total of 1454 patients exposed to s.c. tocilizumab were tested for anti-tocilizumab antibodies. Thirteen patients (0.9%) developed positive anti-tocilizumab antibodies; of these, twelve patients (0.8%) developed neutralising anti-tocilizumab antibodies. Five patients (0.3%) tested positive for IgE isotype antibodies.

No correlation was observed between antibody development and clinical response or adverse events.

Injection site reactions

During the 6-month controlled period of study SC-I, the frequency of injection site reactions was 10.1% (64/631) on weekly s.c. Actemra injections and 2.4% (15/631) on weekly s.c. placebo injections (IC group). These injection site reactions (including erythema, pruritus, pain and haematoma) were mild to moderate in severity. The majority of reactions resolved without treatment and did not require interruption of treatment.

Early rheumatoid arthritis

Study VI (WA19926) evaluated 1162 MTX- and biologic-naïve patients with moderate to severe early RA. Overall, the safety profile in the tocilizumab treatment groups was consistent with the known safety profile of tocilizumab (see Undesirable effects).

In study VI, MTX-naïve adult patients with moderate to severe active early RA (mean disease duration ≤6 months) receiving Actemra in combination with MTX or as monotherapy showed decreased neutrophils and platelets and increased lipid levels more frequently than those given MTX alone. Increases in ALT, AST and bilirubin were also more frequent on the combination of Actemra plus MTX than on MTX alone.

Polyarticular juvenile idiopathic arthritis

The safety profile of intravenous tocilizumab was studied in 188 paediatric patients aged 2 to 17 years with PJIA. Total exposure in the population of all patients exposed to tocilizumab was 184.4 patient-years. In general, the adverse drug reactions in patients

with PJIA were similar in nature to those in RA and SJIA patients (see *Undesirable effects*). *Autoimmune diseases*

Isolated cases of myasthenia gravis, systemic sclerosis and uveitis were observed in the clinical trials. Patients with PJIA in general show a higher risk of autoimmune diseases. The causal relationship to tocilizumab is unclear.

Infections

The most commonly observed events in PJIA were infections. The infection rate in the population of all PJIA patients exposed to i.v. tocilizumab was 163.7 per 100 patient-years. The most common events observed were nasopharyngitis and upper respiratory tract infections.

The serious infection rate of 12.2 per 100 patient-years in patients below 30 kg on 10 mg/kg tocilizumab was numerically higher than in patients below 30 kg on 8 mg/kg tocilizumab (3.7 per 100 patient-years) or in patients ≥30 kg on 8 mg/kg tocilizumab (4.0 per 100 patient-years). The proportion of patients with infections leading to treatment interruptions was also numerically higher in patients <30 kg on 10 mg/kg tocilizumab (21.4%) than in patients ≥30 kg on 8 mg/kg tocilizumab (7.6%).

Infusion reaction

In PJIA patients, infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion of i.v. tocilizumab. In the population of all patients exposed to tocilizumab, 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 occurring 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. No hypersensitivity reactions requiring treatment interruption were reported in association with tocilizumab.

Immunogenicity

One patient (0.5% [1/188] in the i.v. study developed positive neutralising anti-tocilizumab antibodies; without experienced a serious or clinically significant hypersensitivity reaction. No correlation was observed between antibody development and clinical response or adverse events.

Laboratory values in the tocilizumab-exposed PJIA population

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

In patients with PJIA, the laboratory side effect profile was similar to that observed in other studies of Actemra.

Systemic juvenile idiopathic arthritis

The safety profile of intravenous Actemra in SJIA was evaluated in 112 paediatric patients aged 2 to 17 years.

During the phase I study (NP25737), no new or unexpected adverse reactions were observed in eleven paediatric SJIA patients under 2 years old. However, the incidence of

serious hypersensitivity 3/11 (27%), including anaphylaxis, in these patients was higher than in SJIA patients aged 2 years and above.

In general, the adverse drug reactions in patients with SJIA were similar to those observed in patients with RA (see *Undesirable effects* above).

Infections

In the 12-week controlled study (WA18221), the rate of all infections was 344.7 per 100 patient-years in the group treated with i.v. tocilizumab and 287.0 per 100 patient-years in the placebo group.

In the 12-week controlled study (WA18221), the rate of serious infections in the group treated with i.v. tocilizumab was 11.5 per 100 patient-years.

Infusion reaction

In SJIA patients, infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion of i.v. tocilizumab. In the 12-week controlled study (WA18221), such events occurred in four percent (4.0%) of patients in the tocilizumab group during the infusion, with one event (angioedema) considered serious and life-threatening, resulting in discontinuation of the study treatment in that patient.

An event occurred within 24 hours of infusion in 16% of patients in the group treated with i.v. tocilizumab and in 5.4% of patients in the placebo group. In the tocilizumab group, the events included, but were not limited to, rash, urticaria, diarrhoea, epigastric discomfort, arthralgia and headache. One of these events (urticaria) was classified as serious.

Clinically significant hypersensitivity reactions associated with i.v. tocilizumab and requiring treatment discontinuation were reported in 1 of 112 patients (less than 1%) treated with i.v. tocilizumab in the controlled and open-label phases of the clinical trial.

Laboratory values in the tocilizumab-exposed SJIA population

Neutrophils:

During routine laboratory monitoring in the 12-week IV controlled study (WA18221), a decrease in neutrophils to below 1×10^9/L occurred in 7% of patients in the group treated with i.v. tocilizumab and in none of the patients in the placebo group.

In the open-label extension study (WA18221), a decrease in neutrophils to below 1×10^9/L occurred in 15% of patients in the group treated with i.v. tocilizumab.

Platelets:

In SJIA, during routine laboratory monitoring in the 12-week controlled study (WA18221), a decrease in platelets to $\leq 100 \times 10^3$/µL occurred in 3% of patients in the placebo group and in 1% of patients in the group treated with i.v. tocilizumab. In the open-label extension study (WA18221), a decrease in platelets to below 100×10^3/µL occurred without associated bleeding events in 3% of patients in the group treated with i.v. tocilizumab.

Liver enzymes:

During routine laboratory monitoring in the 12-week controlled study (WA18221), an increase in ALT or AST to ≥3 × ULN occurred in 5% and 3% of patients, respectively, in the group treated with i.v. tocilizumab and in 0% of patients in the placebo group.

In the open-label extension study (WA18221), an increase in ALT or AST to ≥3 × ULN occurred, respectively, in 12% and 4.0% of patients in the group treated with i.v. tocilizumab.

Lipid parameters:

In SJIA, during routine laboratory monitoring in the 12-week controlled study (WA18221), an increase in LDL cholesterol to ≥130 mg/dL or in total cholesterol to ≥200 mg/dL occurred in 13.4% and 33.3% of patients, respectively. In the open-label extension study (WA18221), an increase in LDL cholesterol to ≥130 mg/dL or in total cholesterol to ≥200 mg/dL occurred in 13.2% and 27.7% of patients, respectively.

Immunogenicity

In study NP25737, 3 of 11 patients developed treatment-induced anti-tocilizumab antibodies. Of these 3 patients, 2 patients experienced a serious hypersensitivity reaction and 1 patient experienced thrombocytopenia, leading in all cases to discontinuation of treatment. However, due to the small sample size, the low number of events and confounding factors, conclusions could not be drawn**.**

Overdosage

Only limited data are available on Actemra overdosage. One case of accidental overdosage has been reported, in a patient with multiple myeloma who had received a single intravenous dose of 40 mg/kg BW. No adverse effects were observed.

No serious adverse effects were identified in healthy volunteers given single intravenous doses up to 28 mg/kg BW, although dose-limiting neutropenia was observed.

Properties and effects

ATC code: L04AC07

Mechanism of action

Tocilizumab is a recombinant humanised monoclonal IgG1 antibody directed against the human interleukin-6 (IL-6) receptor.

Tocilizumab binds both to the soluble and membrane-bound receptors of IL-6 (sIL-6R and mIL-6R) and inhibits signal transduction. IL-6 is a proinflammatory pleiotropic cytokine produced by many cells, including T and B cells, lymphocytes, monocytes and fibroblasts. IL-6 is involved in various physiological processes such as T cell activation, initiation of Ig secretion by B cells, initiation of acute-phase hepatic protein synthesis, and stimulation of haematopoiesis. IL-6 plays a role in the pathogenesis of diseases such as inflammatory reactions, osteoporosis and cancer.

Pharmacodynamics

Treatment with Actemra in RA patients causes a rapid decrease in C-reactive protein (CRP), erythrocyte sedimentation rate, serum amyloid A, fibrinogen and acute-phase proteins and a reduction in platelet count, as well as an increase in haemoglobin level. IL-6 inhibition increases iron availability by reducing the acute-phase protein hepcidin. In patients treated with Actemra, CRP fell to normal levels by week 2 and subsequently remained stable throughout the treatment period.

Neutropenia with nadir at day 3-6 is observed during treatment with tocilizumab (see *Warnings and precautions*).

Clinical efficacy

Rheumatoid arthritis

Patients receiving treatment with intravenously administered Actemra

Two dose-finding studies evaluated Actemra at doses of 2, 4 and 8 mg/kg every 4 weeks alone or in combination with MTX. Five double-blind controlled phase III studies conducted over periods of 3 to 6 months evaluated Actemra in patients with moderate to severe rheumatoid arthritis (mean Disease Activity Score 28 [DAS28]: 6.5–7) who had failed to respond to prior treatment with one to three DMARDs. The inclusion criterion was a mean disease duration of at least 6 months; median disease duration across all patients was 7–9 years. All patients had previously received MTX at doses ranging from 10 to 25 mg in studies WA17822 and WA17823 or a DMARD in study WA18063. Study WA18062 included patients who had previously also received adjuvant therapy with TNF-alfa inhibitors.

The primary endpoint was the ACR20 score (20% improvement by *American College of Rheumatology* criteria). Secondary endpoints were the ACR50, ACR70, ACRn, DAS28 and EULAR criteria, supplemented by quality of life in some studies. The total number of patients treated with Actemra was 1406, and the total number given disease-modifying therapy with a DMARD was 1010.

The results of these studies at 24 weeks showed Actemra to be effective with respect to the primary endpoint and all other scales employed, both at 4 and 8 mg/kg, better results being achieved with 8 mg/kg tocilizumab.

Another study, WA17824, compared efficacy between tocilizumab and MTX. This trial recruited patients with moderate to severe rheumatoid arthritis who had not taken MTX in the previous 6 months for reasons that did not include poor tolerance or absence of treatment response. Their median disease duration was 3 years. They had taken previous DMARD treatment for a median duration of 1.0 (0–7) years. After an 8-week run-in (in which they were permitted rescue treatment), participants were randomised to either MTX 7.5 mg (subsequently increased to 20 mg) or Actemra 8 mg/kg. Actemra 8 mg/kg was superior to MTX in the primary endpoint of ACR20 at 24 weeks with rates of 70% and 52.5%, respectively. This study revealed marked regional and subgroup differences in ACR20 response rates between the patient groups on MTX and those on tocilizumab: 38% versus 48% in North America and 58% versus 80% in Europe, and better results compared to MTX in patients negative for rheumatoid factor than in those who were factor-positive. There are as yet no data for a period longer than 24 weeks.

Patients continued on treatment in two open-label long-term studies, experience to date over 2 years showing maintained efficacy.

The effect on radiographic progression is documented in two-year data from study WA17823 showing that tocilizumab in combination with MTX significantly reduces radiographic progression (as measured by the Genant-modified Sharp score) compared to placebo and MTX. 83% of patients showed no progression of structural damage on treatment with tocilizumab/MTX versus 67% of placebo/MTX-treated patients.

MTX-naïve, early RA (WA19926)

Study VI was a 2-year study in 1162 MTX-naïve adult patients with moderate to severe active early RA (mean disease duration ≤6 months). The study evaluated the efficacy of combination therapy with intravenous tocilizumab 4 or 8 mg/kg every 4 weeks plus MTX, monotherapy with intravenous tocilizumab 8 mg/kg and MTX monotherapy in reducing the signs and symptoms and rate of progression of joint damage over 104 weeks. The primary endpoint was the proportion of patients with DAS28 remission (DAS28 <2.6) at week 24. Significantly more patients in the tocilizumab 8 mg/kg + MTX and tocilizumab monotherapy groups met the primary endpoint than in the MTX monotherapy group (see Table 1 below for details on 3 of the 4 treatment groups in this study). The tocilizumab 8 mg/kg + MTX group also achieved statistically significant results for the key secondary endpoints.

Table 1: Efficacy results for study VI (WA19926) in MTX-naïve, early RA patients

			TCZ 8 mg/kg + MTX	TCZ 8 mg/kg + placebo	Placebo + MTX
			n=290	n=292	n=287
Primary endpoint					
DAS28 remission					
	Week 24	n (%)	130 (44.8)***	113 (38.7)***	43 (15.0)
Key secondary endpoints					
DAS28 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 (%)		226 (83)‡	226 (82)‡	194 (73)
	(change from baseline in mTSS of ≤0)				

All efficacy comparisons versus placebo + MTX. *** p≤0.0001; ** p<0.001; * p<0.05;

‡ p-value <0.05 versus placebo + MTX.

Monotherapy: Actemra versus adalimumab

In a randomised, double-blind study in 326 RA patients who were intolerant of MTX or in whom continued treatment with MTX was considered inappropriate, intravenous Actemra (TCZ) 8 mg/kg every 4 weeks showed a statistically significant treatment effect in control of disease activity compared to subcutaneous adalimumab (ADA) 40 mg every 2 weeks (primary endpoint DAS28 difference from baseline at week 24: ADA -1.8, TCZ -3.3 95% CI -1.5 [-1.8, -1.1], p<0.0001).

Patients receiving treatment with subcutaneously administered Actemra

The efficacy of subcutaneously administered Actemra was assessed in a double-blind, controlled, multicentre study in patients with active RA. The study (SC-I) enrolled patients aged over 18 years with active rheumatoid arthritis diagnosed according to ACR criteria and at least 4 painful and 4 swollen joints at baseline. All patients received background therapy with one or more non-biological DMARDs.

Study SC-I

Study SC-I evaluated patients with moderate to severe active rheumatoid arthritis who had responded inadequately to their existing rheumatological therapy, including one or more DMARDs. Approximately 20% had responded inadequately to at least one TNF-alpha inhibitor. In study SC-I, 1262 patients were randomised 1:1 to treatment with 162 mg tocilizumab once weekly s.c. or 8 mg/kg tocilizumab every four weeks i.v. in combination with one or more non-biological DMARDs. The primary endpoint of the study was the difference in the proportion of patients who achieved an ACR20 response at week 24. The results of study SC-I are shown in Table 2.

Table 2: Week 24 clinical response in the subcutaneous study (proportion of patients)

	SC-I[a]	
	TCZ 162 mg once weekly s c. + DMARD(s) n=558	TCZ 8 mg/kg i.v. + DMARD(s) n=537
ACR20		
Week 24	69.4%	73.4%
Weighted difference (95% CI)	-4.0 (-9.2, 1.2)	
ACR50		
Week 24	47.0%	48.6%
Weighted difference (95% CI)	-1.8 (-7.5, 4.0)	
ACR70		
Week 24	24.0%	27.9%
Weighted difference (95% CI)	-3.8 (-9.0, 1.3)	
Change in DAS28 [adjusted mean]		
Week 24	3.5	3.5
Adjusted mean difference (95% CI)	0 (-0.2, 0.1)	
DAS28 <2.6		
Week 24	38.4%	36.9%
Weighted difference (95% CI)	0.9 (-5.0, 6.8)	
EULAR response (%)		
No response	3.3%	4.8%
Moderate response	41.7%	42.7%
Good response	55.0%	52.4%

TCZ = tocilizumab
a = Per-protocol population

Study SC-II

Clinical and radiological response to subcutaneously administered Actemra was investigated in a double-blind, controlled, multicentre study in RA patients in combination with methotrexate. This study (SC-II) evaluated patients with moderate to severe active rheumatoid arthritis who had responded inadequately to their existing rheumatological therapy, including one or more DMARDs. Approximately 20% had responded inadequately to at least one TNF inhibitor. The study enrolled patients aged over 18 years with active rheumatoid arthritis diagnosed according to ACR criteria and at least 8 painful and 6 swollen joints at baseline. In study SC-II, 656 patients were randomised 2:1 to treatment with 162 mg tocilizumab once every two weeks s.c. or placebo.

In study SC-II, inhibition of structural joint damage was assessed radiologically and expressed as a change in the van der Heijde-modified mean total Sharp score (mTSS). At week 24, inhibition of structural joint damage was shown, with significantly less progression in patients receiving s.c. tocilizumab compared to placebo (mTSS 0.62 versus 1.23, p=0.0149 [van Elteren]).

The results of study SC-II can be found in Table 3.

Table 3: Week 24 ACR response in study SC-II (% patients)

	SC-II[b]	
	TCZ SC 162 mg every two weeks + DMARD n=437	Placebo + DMARD n=219
Change from baseline Van der Heijde mTSS	0.62	1.23*
ACR20	61%	32%**
ACR50	40%	12%**
ACR70	20%	5%**

TCZ = tocilizumab
mTSS = mean total Sharp score
** p<0.05, tocilizumab versus placebo + DMARD*
*** p<0.0001, tocilizumab versus placebo + DMARD*
[b] Intent-to-treat population

Mean DAS28 at baseline was 6.7 in the patients in the subcutaneous treatment arm and 6.6 in the placebo arm. At week 24 a significant reduction in DAS28 from baseline of 3.1 was observed in the subcutaneous treatment arm, while this value was 1.7 in the placebo arm. A reduction in DAS28 <2.6 was observed in 32% of patients in the subcutaneous treatment arm and 4.0% of patients in the placebo arm.

Polyarticular juvenile idiopathic arthritis

The efficacy of intravenous Actemra was assessed in a phase 3 study including an open-label extension phase in children with active polyarticular juvenile idiopathic arthritis (PJIA) who had failed to tolerate or responded inadequately to MTX. A 16-week open-label Actemra induction phase (n=188) was followed by a 24-week randomised, double-blind, placebo-controlled withdrawal phase (ITT n=163). The subsequent open-label extension phase continued for 64 weeks. The Actemra dose for patients ≥30 kg was 8 mg/kg, while patients <30 kg were compared in two dose groups of 8 mg/kg and 10 mg/kg. Responders following induction (JIA ACR30) entered the placebo-controlled withdrawal phase and received either Actemra at the same dose as during the induction phase or placebo. The analysis in both strata was performed with and without MTX or corticosteroid comedication.

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

After the first 16 weeks of treatment, the proportions of patients with a JIA ACR 30, 50, 70 and 90 response were 89.4%, 83.0%, 62.2% and 26.1%, respectively. After the placebo-controlled withdrawal phase (week 40), the JIA ACR 30, 50 and 70 responses were 74.4%, 73.2% and 64.6%, respectively, compared to 54.3%, 51.9% and 42.0% in placebo-treated patients ($p<0.01$).

During the placebo-controlled phase (week 40), the JIA ACR 30, 50, 70 and 90 responses in Actemra patients comedicated with MTX were higher (79.1%, 77.6%, 67.2% and 47.8%) than in Actemra patients not receiving MTX (53.3%, 53.3%, 53.3% and 33.3%). Response rates were also higher in patients not previously treated with biologics (83.6%, 83.6%, 72.7% and 58.2% versus 55.6%, 51.9%, 48.1% and 18.5%).

Systemic juvenile idiopathic arthritis

In a 12-week double-blind, placebo-controlled study, patients received either intravenous tocilizumab (12 mg/kg in those weighing <30 kg [n=38], 8 mg/kg in those weighing ≥30 kg [n=37]) or placebo infusions (n=37) every 2 weeks. The patients enrolled had disease activity (fever, serositis, rash, splenomegaly) persisting for at least 6 months, with ≥5 active joints or 2 active joints plus fever (>38°C). The joints were assessed by an independent blinded assessor. Corticosteroid dose changes were permitted only on the basis of rules predefined in the study protocol.

The primary endpoint was the proportion of patients with a 30% reduction in JIA ACR (JIA ACR30) at week 12 and no fever in the preceding 7 days. This was achieved in 85% in the tocilizumab arm versus 24.3% on placebo. The secondary endpoints JIA ACR50, JIA ACR70 and JIA ACR90 were met, respectively, by 85.3%, 70.7% and 37.5% of patients receiving tocilizumab. A significant effect was also observed in pain reduction compared to placebo. Twenty-four percent of tocilizumab patients were able to reduce the corticosteroid dose by 20% by week 12.

At baseline, an average of 54.7% of patients had fever and 28% rash, with somewhat higher figures (68.4% and 34.2%) in the group of children weighing less than 30 kg. On treatment with tocilizumab, 85% of patients became fever-free. Lymphadenopathy, splenomegaly and hepatomegaly were present in 9.3%, 5.3% and 6.7% at baseline, and in 5.4%, 1.5% and 0% after 12 weeks of treatment with tocilizumab. As well as CRP and ESR, Hb level, platelet count and serum amyloid A also improved in patients with abnormal baseline values. Quality of life improvement, as measured by the CHAQ-DI score, was 77% on tocilizumab and 19% on placebo.

A descriptive, multicentre, open-label, single-arm, phase I study (NP25737) was conducted to evaluate the PK, safety and exploratory PD and efficacy of tocilizumab over 12 weeks in paediatric SJIA patients (n=11) under 2 years of age. Patients (treated with stable background therapy of corticosteroids, MTX or non-steroidal anti-inflammatory drugs) received intravenous tocilizumab 12 mg/kg every two weeks. On completing the 12-week treatment, patients could take part in the optional extension period (total of 52 weeks or until the age of 2 years).

For information on safety results, please refer to *Undesirable effects*.

The exploratory efficacy results showed that tocilizumab improved the median JADAS-71 score over the course of the study for all patients.

Pharmacokinetics

Tocilizumab pharmacokinetics (PK) are characterised by non-linear elimination combining linear clearance and Michaelis-Menten elimination kinetics. The non-linear part of tocilizumab elimination results in a greater than dose-proportional increase in exposure. 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 with serum concentration. In no patient population studied to date have population pharmacokinetic analyses shown an association between apparent clearance and the presence of anti-drug antibodies.

Rheumatoid arthritis

The pharmacokinetic data in healthy subjects and RA patients suggest similar pharmacokinetics in the two groups.

The table below shows model predictions for secondary PK parameters in each of the four approved dosing regimens. The population pharmacokinetic (popPK) model was developed using an analysis database composed of a database of 1793 i.v. treated patients from studies WA17822, WA17824, WA18062 and WA18063 and a database of 1759 i.v. and s.c. treated patients from studies WA22762 and NA25220. The table includes Cmean values since, for dosing regimens with varying intervals between doses, the mean concentration in the dosing interval describes comparative exposure better than the integral or AUCτ value.

Table 4: Prognostic PK parameters (mean ± SD) at steady state after i.v. and s.c. dosing in RA

	i.v.		s.c.	
TCZ PK parameter	**4 mg/kg q4w**	**8 mg/kg q4w**	**162 mg q2w**	**162 mg qw**
C_{max} (µg/ml)	83.8 ± 23.1	182 ± 50.4	13.2 ± 8.8	49.8 ± 21.0
C_{trough} (µg/ml)	0.5 ± 1.5	15.9 ± 13.1	5.7 ± 6.8	43.0 ± 19.8
C_{mean} (µg/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 i.v. administration, 2 weeks or 1 week for the two regimens with s.c. administration

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 the peak concentration (Cmax) increased in proportion to dose at doses between 4 and 8 mg/kg i.v. every 4 weeks, the mean concentration (Cmean) and trough concentration (Ctrough) showed greater than dose-proportional increases. Steady-state Cmean and Ctrough after administration of 8 mg/kg were 3.2 and 32 times higher,

respectively, than after administration of 4 mg/kg. Exposure after administration of 162 mg s.c. qw was 4.6 (Cmean) to 7.5 times (Ctrough) higher than after administration of 162 mg s.c. q2w.

The accumulation ratios after multiple doses of 4 and 8 mg/kg q4w are low for AUC and Cmax, but higher for Ctrough (2.62 and 2.47). The accumulation ratios following multiple dosing were higher with every subcutaneous treatment regimen than after i.v. administration, with the highest ratios obtained for Ctrough (6.02 and 6.30). The higher accumulation for Ctrough was expected, given the influence of non-linear clearance at lower concentrations.

Based on Cmax, over 90% of steady-state concentration was reached after the first i.v. infusion, after the twelfth s.c. injection in the qw dosing regimen and after the fifth s.c. injection in the q2w dosing regimen. Based on AUCτ and Cmean, 90% of steady-state concentration was reached after the first i.v. infusion of 4 mg/kg and after the third i.v. infusion of 8 mg/kg, and after the sixth s.c. injection of 162 mg in the q2w dosing regimen and after the twelfth s.c. injection of 162 mg in the qw dosing regimen. Based on Ctrough, approximately 90% of steady-state concentration was reached after the fourth i.v. infusion and after the sixth and twelfth s.c. injection, respectively.

The population pharmacokinetic analysis identified body weight as a significant covariate influencing tocilizumab pharmacokinetics. Following intravenous administration, subjects weighing ≥100 kg would therefore be likely to have mean steady-state concentrations (based on mg/kg) exceeding the patient population means. Consequently, patients ≥100 kg should not receive tocilizumab doses greater than 800 mg per infusion (see Dosage and administration). Because of the fixed dosing employed with s.c. tocilizumab administration, dose adjustments are not required with this route of administration.

Absorption

After subcutaneous administration to RA patients, the absorption half-life was approximately 4 days. The bioavailability for the s.c. formulation is 0.8.

Distribution

The volume of distribution at steady state was 6.4 L in adult RA patients, 4.01 L in SJIA patients and 4.08 L in PJIA patients.

Elimination

Clearance is concentration-dependent and consists of a linear and a non-linear component. At concentrations >50 µg/mL, non-linear clearance is saturated and clearance is mainly determined by linear clearance. Estimated linear clearance was 12.5 mL/h in adult RA patients, and 5.7 mL/h and 5.8 mLl/h in paediatric patients with SJIA and PJIA, respectively.

Due to the dependence of total clearance on tocilizumab serum concentrations, the $t_{1/2}$ of tocilizumab is also concentration-dependent and can only be calculated at a given serum concentration.

The apparent $t_{½}$ of intravenously administered tocilizumab at steady state in adult RA patients receiving 8 mg/kg every 4 weeks is 13 days.

After subcutaneous administration, concentration-dependent $t_{1/2}$ in RA patients at steady-state is up to 13 days for the 162 mg s.c. once weekly dosage and 5 days for the 162 mg s.c. alternate-week dosage. During administration of 162 mg s.c. weekly and every two weeks, 90% of steady state was reached after the 12th and 6th injection, respectively. At high serum concentrations, when total clearance of tocilizumab is dominated by linear clearance, a terminal $t_{1/2}$ of approximately 21.5 days was determined from the population parameter estimates.

The effective half-life of i.v. tocilizumab during a dosing interval at steady state in the two body weight categories (8 mg/kg for body weight ≥30 kg or 10 mg/kg for body weight <30 kg) is up to 17 days in children with PJIA and up to 23 days in children with SJIA.

Pharmacokinetics in special patient populations

Renal impairment

There have been no pharmacokinetic studies of tocilizumab in patients with renal impairment.

Hepatic impairment

There have been no pharmacokinetic studies of tocilizumab in patients with hepatic impairment.

Children and adolescents with SJIA

The pharmacokinetics of tocilizumab were determined by population pharmacokinetic analysis of a database of 75 SJIA patients treated with 8 mg/kg (patients weighing ≥30 kg) or 12 mg/kg (patients weighing less than 30 kg) once every 2 weeks.

Table 5: Predicted PK parameters (mean ± SD) at steady state after i.v. dosing in SJIA

	i.v.	
TCZ PK parameter	**8 mg/kg q2w ≥30 kg**	**12 mg/kg q2w below 30 kg**
C_{max} (µg/mL)	256 ± 60.8	274 ± 63.8
C_{trough} (µg/mL)	69.7 ± 29.1	68.4 ± 30.0
C_{mean} (µg/mL)	119 ± 36.0	123 ± 36.0
Accumulation C_{max}	1.42	1.37
Accumulation C_{trough}	3.20	3.41
Accumulation C_{mean} or AUC_{τ} *	2.01	1.95

* τ = 2 weeks for the i.v. regimen.

On i.v. treatment with both 12 mg/kg and 8 mg/kg q2w, approximately 90% of steady state was reached at week 8.

The primary PK endpoints (C_{max}, C_{min} and AUC_{2weeks}) for TCZ at steady-state in this study were each within the ranges of values measured in paediatric patients aged 2 to 17 years weighing <30 kg who were treated with the same tocilizumab dose regimen (12 mg/kg i.v. every 2 weeks) in study WA18221.

Children and adolescents with PJIA

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis involving 188 patients with PJIA who were treated with 8 mg/kg i.v. every 4 weeks (patients weighing ≥30 kg), 10 mg/kg i.v. every 4 weeks (patients weighing below 30 kg).

Table 6: Predicted PK parameters (mean ± SD) at steady state after i.v. dosing in PJIA

	i.v.	
TCZ PK parameter	**8 mg/kg every 4 weeks ≥30 kg**	**10 mg/kg every 4 weeks below 30 kg**
C_{max} (µg/mL)	183 ± 42.3	168 ± 24.8
C_{trough} (µg/mL)	6.55 ± 7.93	1.47 ± 2.44
C_{mean} (µg/mL)	42.2 ± 13.4	31.6 ± 7.84
Accumulation ratio C_{max}	1.04	1.01
Accumulation ratio C_{trough}	2.22	1.43
Accumulation ratio C_{mean} or AUC_{τ} *	1.16	1.05

* τ = 4 weeks for the i.v. regimens.

Preclinical data

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

No carcinogenicity or fertility studies of tocilizumab have been performed in the absence of a model that can be used for antibodies that do not react with rodent IL-6 receptors.

Available preclinical data have shown that IL-6 contributes to malignant progression and apoptosis resistance of various cancer types and suggested that a relevant risk of cancer initiation and/or growth cannot be entirely excluded on tocilizumab therapy. A 6-month toxicity study in Rhesus monkeys and IL-6 knock-out mice showed no evidence of proliferative lesions.

The available preclinical data suggest that treatment with tocilizumab has no influence on fertility. No effect on endocrine activity or reproductive system organs was observed in a toxicity study in rhesus monkeys. Reproductive function was unaffected in IL-6 knock-out mice.

Tocilizumab administered to Rhesus monkeys during early pregnancy was observed to have no direct or indirect harmful effect on pregnancy or embryo-foetal development. However, a slight increase in abortion/embryo-foetal death was observed at high systemic concentrations (over 100 times the concentration in humans) on cumulative administration of 50 mg/kg BW compared to placebo or lower doses. Although IL-6 does not seem to play a critical role in foetal growth or immunological control of the maternal/foetal interface, an interaction with tocilizumab cannot be excluded.

Excretion in milk was observed in lactating mice after a single intravenous treatment with a murine tocilizumab surrogate antibody.

Treatment of juvenile mice with a murine analogue caused no toxicity, and in particular no impairment of skeletal growth, immune function or sexual maturation. The non-clinical safety profile of tocilizumab in cynomolgus monkeys does not suggest a difference between the i.v. and s.c. routes of administration.

Preclinical tests have not been performed with the combination of tocilizumab and MTX.

Additional information

Incompatibilities

Intravenous formulation

Actemra must not be mixed with other medicinal products apart from the 0.9% sodium chloride solution mentioned in *Instructions for handling*. No incompatibilities have been found between Actemra and polyvinyl chloride, polyethylene or polypropylene infusion bags or sets.

Subcutaneous formulation

Actemra must not be mixed with other medicinal products.

Stability

This medicinal product must not be used after the expiry date (EXP) shown on the container.

Intravenous administration

After dilution in 0.9% (w/v) sodium chloride solution, chemical and physical in-use stability of the solution for infusion has been demonstrated for 24 hours at 30°C.

Since the dilute solution for infusion contains no preservatives, microbiological considerations require it to be used immediately after preparation. If it cannot be administered directly, storage times and conditions become the user's responsibility and should not normally exceed 24 hours at 2–8°C, except if dilution was performed under controlled and validated aseptic conditions.

Subcutaneous administration

Before use the prefilled syringe should be taken from the refrigerator and kept outside the carton at room temperature (15-25°C) for at least 25-30 minutes. Do not store above 30°C. Once removed from the refrigerator, the injection solution should be administered within 8 hours.

Special instructions for storage

Intravenous administration

Store concentrate in a refrigerator (2–8°C).

Do not freeze.

Keep the container in the outer carton in order to protect the contents from light.

Subcutaneous administration

Store prefilled syringe in a refrigerator at 2-8°C. Do not freeze. Keep in outer carton to protect the contents from light.

Instructions for handling

Intravenous administration:

Actemra is supplied in pyrogen-free single-use vials containing no preservatives.

1) Withdraw the required volume of Actemra (a dose of 8 mg/kg BW corresponds to 0.4 ml/kg BW, 10 mg/kg to 0.5 ml/kg and 12 mg/kg to 0.6 ml/kg) from one or more unopened vials under aseptic conditions using a separate unused syringe. Discard any unused portion left in the vial.
2) Using another unused syringe, discard the same volume of isotonic sodium chloride solution (sterile, pyrogen-free 0.9% [w/v] sodium chloride solution) as the required volume of Actemra from a 100 ml infusion bag (for patients ≥ 30 kg) or from a 50 ml infusion bag (for PJIA or SJIA patients < 30 kg).
3) Under aseptic conditions, add the previously withdrawn volume of Actemra to the 100 ml or 50 ml infusion bag mentioned above. The preparation now contains the required quantity of Actemra in a total volume of 100 ml or 50 ml 0.9% sodium chloride solution.

4) Mix the solution well by inverting the infusion bag gently to avoid foaming.
5) Medicinal products for parenteral administration should be visually inspected before use for particulate matter or discolouration.
   Only solutions that are clear to opalescent, colourless or light yellow and free of suspended particulate matter may be used for infusions.
6) Discard any unused drug (concentrate or dilute solution for infusion) and dispose of according to current regulations.

Disposal of unused or expired medicinal products
The release of pharmaceutical preparations into the environment should be reduced to a minimum. Medicinal products should not be disposed of via the wastewater system and disposal in domestic waste should be avoided. Any medicinal products unused after the end of treatment or by the expiry date should be returned in their original packaging to the place of supply (physician or pharmacist) for proper disposal.

Subcutaneous administration

Do not use if the solution is cloudy, contains particles or is discoloured (i.e. not colourless or yellowish), or if any part of the prefilled syringe or needle safety device appears to be damaged.

Once the needle cover is removed, the syringe must be used **immediately (within max. 5 minutes)**.

Disposal of materials

Patients should be made aware that the following points must be strictly followed when using and disposing of the prefilled syringe and needle safety device:

- Pre-filled syringes must not be reused.
- All used syringes must be discarded in a puncture-proof disposable sharps container.
- Keep containers away from children.
- Do not dispose of used sharps containers in household waste, but according to the doctor's or pharmacist's instructions.

For home use, patients should provide a sharps container for disposal of used syringes.

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.
Do not repeat the same prescription without consulting your doctor.

Packs

Concentrate for solution for infusion
Vials of solution for dilution for infusion
– 4 ml solution (20 mg/ml) containing 80 mg: 1
– 10 ml solution (20 mg/ml) containing 200 mg: 1
– 20 ml solution (20 mg/ml) containing 400 mg: 1

Injection solution for subcutaneous administration
0.9 ml (162 mg) single-use prefilled syringe with needle safety device: 4

Medicine: keep out of reach of children

Current at August 2019

Vials:

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland
by Chugai Pharma Manufacturing Co., Ltd, Utsunomiya City, Japan

Pre-filled syringes:

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland
by Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany