Actemra®

Tocilizumab

Composition

Active substance

Tocilizumab.

Excipients

Concentrate for solution infusion:

Sucrose, polysorbate 80, disodium phosphate dodecahydrate, monosodium phosphate dihydrate, water for injections.

Injection 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

Solution for dilution 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 to reduce signs and symptoms in adult patients with moderate to severe active rheumatoid arthritis who have failed to respond adequately to treatment with disease-modifying antirheumatic drugs (DMARDs) or tumour necrosis factor (TNF) inhibitors. Combination therapy with methotrexate (MTX) has been shown to slow progression of structural damage and improve physical function. Actemra may be used alone or in combination with methotrexate and/or other standard DMARDs.

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 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 formulation

Actemra therapy must be administered under the supervision of a physician with experience in managing patients with active 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 remarks, Instructions for handling*).

Actemra is administered as an intravenous infusion over 1 hour.

Subcutaneous formulation

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. The patient's suitability for s.c. home use must be assessed. Patients must be instructed to inform a healthcare professional before administering the next dose if they experience symptoms of a serious allergic reaction (see *Warnings and precautions*).

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.

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 kg should not receive single doses exceeding 800 mg.

The i.v. formulation of Actemra is not intended for subcutaneous administration.

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.

Patients switching from i.v. Actemra 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 s.c. formulation of Actemra is not intended for intravenous administration.

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])

Patients with PJIA are given Actemra as an i.v. infusion.

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 <30 kg who have not responded to the recommended standard dose of 8 mg/kg after 8 weeks. The dose should be adjusted for long-term weight changes during growth.

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

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

Patients with SJIA are given Actemra as an i.v. infusion.

The recommended dose is:

- 12 mg/kg for patients weighing <30 kg
- 8 mg/kg for patients weighing ≥30 kg

once every two weeks (intravenous infusion over 1 hour).

Special dosage instructions

Use in children and adolescents

The safety and efficacy of Actemra have not been evaluated in children and adolescents with joint diseases other than PJIA or SJIA. Children under two years old have not been studied.

Use in elderly (≥65 years)

No dose adjustment is necessary.

Patients with renal impairment

No dose adjustment is required in patients with mild 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 or reduced neutrophil or platelet counts

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

For transaminase levels up to 3 times the upper limit of normal (ULN), it is recommended that the dose of coadministered MTX be reduced and, if elevation persists, that the Actemra dose be reduced to 4 mg/kg; if levels remain high, Actemra should be temporarily withheld until the values return to normal.

For transaminase levels 3-5 × ULN or decreases in neutrophil count to 0.5-1 × 10^9/l or in platelet count to 50-100 × 10^9/l, it is recommended that Actemra be temporarily withheld until stabilisation of transaminase levels at <3 × ULN, neutrophils at >1 × 10^9/l and platelets at >100 × 10^9/l. Thereafter, treatment with Actemra may be resumed at 4 mg/kg and should be increased to the approved dose of 8 mg/kg. For transaminase levels >5 × ULN or decreases in neutrophil count to <500/µl or in platelet count to <50,000/µl, Actemra should be permanently discontinued.

Contraindications

Known hypersensitivity to the active substance or to 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

In order to improve the traceability of biologicals, the tradename Actemra must be clearly entered in the patient's record. Replacement by another biological requires the consent of the prescribing physician. Data in this prescribing information relate only to Actemra.

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. In patients with recurrent infections or in those with disease predisposing to infection (for example, diverticulitis or diabetes), treatment should be administered with caution.

It is recommended that treatment be monitored to aid timely recognition of severe infection since the signs and symptoms of acute inflammation may be muted. Patients and parents/carers of children and adolescents with PJIA or SJIA should be advised to contact their doctor promptly about symptoms suggestive of infection to enable the requisite investigations to be undertaken without delay and appropriate treatment instituted.

Immunosuppression

Actemra therapy may impair the humoral immune response.

Complications of diverticulitis

Cases of diverticular perforation have been reported in adults as a complication of diverticulitis. 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

Before initiating Actemra therapy a work-up should be undertaken for latent tubercular infection. Patients with latent tuberculosis should receive standard antimycobacterial therapy before being started on Actemra.

Hypersensitivity reactions

In the postmarketing setting, events of serious hypersensitivity and anaphylaxis, including 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 “What you should know about Actemra”, doctor’s brochure “Important efficacy and safety information” and “Dosage and administration guide”). In the event of hypersensitivity reactions, patients must inform their doctor immediately and, if necessary, seek emergency treatment.

Active hepatic disease and hepatic impairment

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.

In the clinical trials, a mild to moderate, transient and sometimes recurrent increase was observed in transaminases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) during Actemra therapy, without resulting in chronic hepatic impairment. This

increase was more often observed when potentially hepatotoxic drugs (for example, MTX) were used in combination with Actemra.

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

In adult RA patients, transaminase levels should be checked 4–8 weeks after starting treatment, then as often as considered necessary by the attending physician.

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

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: with persistently elevated levels in this range should reduce the injection schedule to once every two weeks or interrupt treatment with tocilizumab 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 several occasions, Actemra therapy should be discontinued. 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.

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 data are available on the safety of such combinations.

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 viremia or the effects on vaccine reactions after active vaccination. Antibody production in 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 children and adolescents with PJIA or SJIA, 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 8 mg/kg BW combined with standard DMARDs.

In patients with a low neutrophil or platelet count (i.e. absolute counts of $<2 \times 10^9$/l and $<100 \times 10^9$/l, respectively), caution must be observed when initiating Actemra therapy. Treatment should be withheld in patients with absolute counts of $<0.5 \times 10^9$/l neutrophils or $<50 \times 10^9$/l platelets.

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

Neutrophils

Patients receiving treatment with intravenous 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 $>1 \times 10^9$/l, Actemra therapy can be reintroduced at the reduced dosage of 4 mg/kg BW. Return to the dose of 8 mg/kg BW is recommended only when clinically indicated.

Patients receiving treatment with subcutaneous Actemra:

As soon as the neutrophil count returns to $>1 \times 10^9$/l, treatment can be resumed with an alternate-week injection schedule, and this 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.

Patients receiving treatment with intravenous Actemra:

As soon as the platelet count returns to $>100 \times 10^9$/l, Actemra therapy can be reintroduced at the reduced dosage of 4 mg/kg BW. Return to the dose of 8 mg/kg BW is recommended only when clinically indicated.

Patients receiving treatment with subcutaneous Actemra:

As soon as the platelet count returns to $>100 \times 10^9$/l, treatment can be resumed with an alternate-week injection schedule, and this increased to once weekly when clinically feasible.

Malignancy

Patients with rheumatoid arthritis are at increased risk of malignancy. Although it is not possible to calculate the incidence of malignancy after Actemra administration from the available clinical data, there is no indication from these data that the risk is increased. The results of the long-term safety studies are not yet available.

Cardiovascular risks

Patients with rheumatoid arthritis are at increased risk of cardiovascular disease. This applies in particular to patients with risk factors such as hypertension, dyslipidemia and diabetes in whom close monitoring (ECG, blood pressure) is mandatory.

Activation of the complement system

Although potential activation of the complement system on Actemra therapy cannot be excluded, the preclinical and clinical data currently available give no indication that this might occur.

Lipid parameters

Elevations in lipid parameters such as total cholesterol, triglycerides and/or low density lipoprotein (LDL) have been observed.
In adult RA patients and patients with PJIA or SJIA, 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 hyperlipidemia.

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 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)], analgesics [paracetamol, tramadol, codeine and derivatives]). Coadministration of a single dose of

10 mg/kg tocilizumab 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 (for example, 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-fetal 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 ability to drive and use machines. However, there is no evidence that treatment with Actemra affects the ability to drive or use machines.

Undesirable effects

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.

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 in the treatment arms with i.v. administration (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.
Adverse effects have been classified by organ type and incidence into the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); not known (frequency cannot be determined from post-marketing experience).

Immune system disorders

Common: hypersensitivity reactions
Uncommon: anaphylactic reactions (some fatal) (see *Warnings and precautions).*

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).

Disorders of the blood and lymphatic circulation
Common: leukopenia, neutropenia
Uncommon: thrombocytopenia

Endocrine disorders
Uncommon: hypothyroidism

Metabolic and nutritional disorders
Common: hypercholesterolemia
Uncommon: hypertriglyceridemia

Nervous system disorders
Common: headache, dizziness

Eyes
Common: conjunctivitis

Vascular disorders
Common: hypertension

Respiratory organs
Common: cough, dyspnea

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

Hepatobiliary disorders
Common: increase in transaminases
Uncommon: increase in total bilirubin

Skin disorders
Common: cellulitis, rash, pruritus, urticaria

Frequency not known: Stevens-Johnson syndrome (SJS) has been reported to occur on treatment with tocilizumab.

Kidneys and urinary tract
Uncommon: nephrolithiasis

Administration site reactions
Common: peripheral edema, injection site reaction

Investigations
Common: weight gain

Immunogenicity

RA patients: 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.

SJIA patients: All 112 patients investigated in the pediatric clinical studies were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti-tocilizumab antibodies; one of these patients had a hypersensitivity reaction that led to withdrawal from the study.

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

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 (IV group). The injection site reactions (including

erythema, pruritus, pain and hematoma) were mild to moderate in severity. The majority of reactions resolved without treatment and did not require interruption of treatment.

Polyarticular juvenile idiopathic arthritis

The safety of intravenous tocilizumab was studied in 188 pediatric 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*). Safety-related treatment discontinuations were seen in one of 28 patients in the 10 mg/kg (<30 kg) group, one of 34 patients in the 8 mg/kg (<30 kg) group and in three of 119 patients in the 8 mg/kg (≥30 kg) group.

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 infection rate in the population of all patients exposed to 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 <30 kg on 10 mg/kg tocilizumab was numerically higher than in patients <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. 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.

Laboratory values in the tocilizumab-exposed PJIA population

A decrease in neutrophil count below 1×10^9/l occurred in 3.7% of patients. There was no clear relationship between decreases in neutrophils below 1×10^9/l and the occurrence of serious infections. One percent of patients had a decrease in platelet count to $\leq 50 \times 10^9$/l without associated bleeding events. Elevation in ALT or AST ≥3 × ULN occurred in 3.7% and <1% of tocilizumab-exposed PJIA patients, respectively. Elevation in total cholesterol >1.5-2 × ULN and elevation in LDL >1.5-2 × ULN each occurred in one patient (0.5%).

Systemic juvenile idiopathic arthritis

The safety of intravenous Actemra in SJIA was evaluated in 112 pediatric patients aged 2 to 17 years. In the 12-week double-blind, controlled portion of the clinical study, 75 patients received treatment with Actemra (8 or 12 mg/kg, depending on body weight). After 12 weeks or on the occurrence of an escape phenomenon due to disease worsening, patients were treated in the ongoing open-label extension phase.

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

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 effect was observed.

In healthy volunteers given single intravenous doses up to 28 mg/kg BW, no serious adverse effects were observed and one case of dose-dependent neutropenia was reported.

Properties and effects

ATC code: LO4AC07

Mechanism of action

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

Tocilizumab binds both to the soluble and membrane-bound receptors of IL-6 (sIL-6R and mIL-6R) and inhibits signal transmission. IL-6 is a proinflammatory pleiotropic cytokine produced by many cells, including T and B cells, lymphocytes, monocytes and fibroblasts. IL-6 intervenes 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 hematopoiesis. IL-6 plays a role in the pathogenesis of diseases such as inflammatory reactions, osteoporosis and cancer.

Pharmacodynamics

Treatment with Actemra causes a rapid decrease in C-reactive protein (CRP), erythrocyte sedimentation rate, serum amyloid A protein, acute-phase proteins and platelet count, as well as an increase in the hemoglobin level. IL-6 inhibition causes an increase in the availability of iron due to a decrease in the levels of hepcidin, an acute-phase protein. In patients on Actemra therapy, CRP levels became normal 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 the effect of Actemra at the 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 the effects of 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 of those received disease-modifying therapy with a DMARD was 1010.

The results of these studies at 24 weeks showed Actemra to be effective with respect both to the primary endpoint and the other scales used for this purpose, whether at the 4 or 8 mg/kg dose, the best 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 stopped taking 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 stand-by treatment), participants were randomised either to MTX 7.5 mg (subsequently increased to 20 mg) or Actemra 8 mg/kg. The fact that 70% of Actemra patients achieved the primary endpoint, an ACR20 score at 24 weeks, versus 52.5% of MTX patients established Actemra 8 mg/kg as the superior treatment.

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 methotrexate significantly reduces radiographic progression (as measured by the Genant-modified Sharp score) compared to placebo and methotrexate. 83% of patients showed no progression of structural damage on treatment with tocilizumab/MTX versus 67% of placebo/MTX-treated patients.

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 >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 randomized 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 1.

Table 1 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 >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 2.

Table 2 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.

Pharmacokinetics

Absorption

Intravenous administration

Tocilizumab elimination from the circulation is biphasic after intravenous infusion. The following parameters characterise tocilizumab when administered at a dose of 8 mg/kg BW every 4 weeks: mean (± SD) steady-state area under the curve (AUC) 35,000 ± 15,500 h × µg/ml, C_{min} 9.74 ± 10.5 µg/ml and C_{max} 183 ± 85.6 µg/ml. Accumulation ratios were low: 1.22 in the case of the AUC and 1.06 in the case of C_{max}. The

accumulation ratio was higher (2.35) in the case of C_{min} (due to the higher proportion of non-linear clearance at low concentrations). Steady state was reached after the first dose in the case of C_{max}, after 8 weeks in the case of the AUC and after 20 weeks in the case of C_{min}.
Tocilizumab AUC, C_{min} and C_{max} increased with body weight. At body weight ≥100 kg the predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 55,500 ± 14,100 µg × h/ml, 19.0 ± 12.0 µg/ml and 269 ± 57 µg/ml, respectively, which are higher than mean exposure values for the patient population. For this reason tocilizumab doses exceeding 800 mg per infusion are not recommended for patients weighing ≥100 kg (see *Dosage and administration*).

The following parameters apply to a dose of 4 mg/kg tocilizumab given every 4 weeks: mean (± SD) AUC of tocilizumab at steady state was 13,000 ± 5800 h × µg/ml, C_{min} 1.49 ± 2.13 µg/ml and C_{max} 88.3 ± 41.4 µg/ml. The accumulation ratios for AUC and C_{max} were low, at 1.11 and 1.02, respectively. The accumulation ratio was higher for C_{min} (1.96). Steady state was reached after the first dose for C_{max} and AUC and after 16 weeks for C_{min}.

Subcutaneous administration:

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis of a database composed of 1759 rheumatoid arthritis patients treated with 162 mg once weekly s.c., 162 mg every two weeks s.c. or 8 mg/kg every four weeks for 24 weeks.

The pharmacokinetic parameters of tocilizumab did not change over time. For the 162 mg once weekly dosage, the predicted mean (±SD) steady-state AUC_{1week}, C_{min} and C_{max} of tocilizumab were 8200 ± 3600 µg × h/ml, 44.6 ± 20.6 µg/ml and 50.9 ± 21.8 µg/ml, respectively. The accumulation ratios for AUC, C_{min} and C_{max} were 6.83, 6.37 and 5.47, respectively. Steady state was reached after 12 weeks for AUC, C_{min} and C_{max}.

For the 162 mg s.c. alternate-week dosage, the predicted mean (±SD) steady-state AUC_{1week}, C_{min} and C_{max} of tocilizumab were 3200 ± 2700 µg × h/ml, 5.6 ± 7.0 µg/ml and 12.3 ± 8.7 µg/ml, respectively. The accumulation ratios for AUC, C_{min} and C_{max} were 2.67, 5.6 and 2.12, respectively. Steady state was reached after 12 weeks for AUC and C_{min} and after 10 weeks for C_{max}.

After s.c. administration to rheumatoid arthritis patients, the absorption half-life was approximately 4 days. Due to the non-linear pharmacokinetics of tocilizumab, the absolute bioavailability of subcutaneous use at steady state is higher than after single-dose administration (77% versus 57%).

Distribution

The volume of distribution at steady state was 6.4 l in adult RA patients, 2.54 l in SJIA patients and 4.08 l in PJIA patients.

Elimination

Clearance is concentration-dependent and consists of a linear and 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 7.1 ml/h and 5.8 ml/h in pediatric patients with SJIA and PJIA, respectively.

The elimination half-life ($t_{½}$) of intravenously administered tocilizumab is accordingly also concentration dependent. The apparent $t_{½}$ at steady state in adult RA patients receiving 8 mg/kg every 4 weeks is 13 days.
The $t_{1/2}$ in children with PJIA or SJIA is up to 23 and 16 days, respectively.

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.

Pharmacokinetics in special patient groups

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 <30 kg) once every 2 weeks. The predicted mean (± SD) $AUC_{2\ weeks}$, C_{max} and C_{min} of tocilizumab were 32,200 ± 9960 µg·h/ml, 245 ± 57.2 µg/ml and 57.5 ± 23.3 µg/ml, respectively. The accumulation ratio for C_{min} (week 12/week 2) was 3.2 ± 1.3. Tocilizumab C_{min} was stable from week 12 onwards. Mean predicted tocilizumab exposure parameters were similar between the two body weight groups. Tocilizumab $t_{½}$ in children with SJIA is up to 23 days in both body weight classes (8 mg/kg for body weight ≥30 kg and 12 mg/kg for body weight <30 kg) at week 12.

Children and adolescents with PJIA

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis involving 188 patients with PJIA.

The following parameters apply to a dose of 8 mg/kg tocilizumab (patients weighing ≥30 kg) given every 4 weeks. The predicted mean (± SD) $AUC_{4\ weeks}$, C_{max} and C_{min} of tocilizumab were 29,500 ± 8660 µg·h/ml, 182 ± 37 µg/ml, and 7.49 ± 8.2 µg/ml, respectively.

The following parameters apply to a dose of 10 mg/kg tocilizumab (patients weighing <30 kg) given every 4 weeks. The predicted mean (± SD) $AUC_{4\ weeks}$, C_{max} and C_{min} of

tocilizumab were 23,200 ± 6100 µg·h/ml, 175 ± 32 µg/ml and 2.35 ± 3.59 µg/ml, respectively.

Preclinical data

Preclinical studies based on conventional pharmacological screening (safety, repeated-dose toxicity and genotoxicity) have shown no evidence of particular danger 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.

The available preclinical data show that IL-6 intervenes in the progression and resistance to apoptosis of various types of tumour, thus suggesting that on tocilizumab therapy the risk of tumour initiation and/or growth cannot definitely be excluded. 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-fetal development. However, a slight increase in abortion/embryo-fetal death was observed at high systemic concentrations (>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 fetal growth or immunological control of the maternal/fetal 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 methotrexate.

Additional remarks

Incompatibilities

Intravenous formulation:

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

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 extends to 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; storage should not normally exceed 24 hours at 2–8°C, except if dilution was performed under controlled and validated 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 that of the required volume of Actemra from a 100 ml infusion bag (for patients ≥ 30 kg) or a from 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 intended for parenteral administration should be visually inspected for particulate matter or discoloration.
   Only solutions that are clear, opalescent, colourless or light yellow and free of suspended particulate matter may be used for infusions.
6) Discard any residual drug (concentrate or dilute solution for infusion) and dispose of according to current operating procedures.

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:

- 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.

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 January 2015

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