# Actemra®

Tocilizumab

## Composition

*Active substance*

Tocilizumab.

*Excipients*

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

## 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)

## Indications and potential uses

Actemra is indicated to reduce signs and symptoms in adult patients with moderate to severe active rheumatoid arthritis (RA) 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.
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

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 preparation*).

**Adults (rheumatoid arthritis)**

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

Actemra should be diluted under strictly aseptic conditions by qualified healthcare professionals in a sterile and pyrogen-free solution of 0.9% (w/v) sodium chloride to a total volume of 100 ml.
Patients weighing more than 100 kg should not receive single doses exceeding 800 mg.

**Children and adolescents: 2–18 years (systemic juvenile idiopathic arthritis [SJIA])**
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 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. For this reason, there is no dosage recommendation (see also *Warnings and precautions*).

*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

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

### 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 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).

**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 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 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. If elevation >1–3 × ULN persists despite these measures, the dose of Actemra must be adjusted in order to normalise the ALT/AST levels.

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 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 $<100 \times 10^3$/µl, 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 $<50 \times 10^3$/µl platelets.

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

If the neutrophil count falls below $1 \times 10^9$/l but continues to exceed $0.5 \times 10^9$/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.

If the platelet count falls below $100 \times 10^3$/µl but continues to exceed $50 \times 10^3$/µl, treatment should be suspended. As soon as the platelet count returns to $>100 \times 10^3$/µl, 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.

**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 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 interleukin-6 (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/embryofetal 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

It is not known whether Actemra is excreted in human milk. Excretion of a tocilizumab surrogate antibody in milk has been demonstrated in mice (see *Preclinical data*).

## Effects on ability to drive and operate machinery

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

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.

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)

*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
Uncommon: diverticulitis, gastrointestinal perforation

*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

*Investigations*
Common: weight gain

**Immunogenicity**

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

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.

### Systemic juvenile idiopathic arthritis

The safety of 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 few data exist on Actemra overdosage. One case of accidental overdosage has been reported, in a patient with multiple myeloma who had received a single dose of 40 mg/kg BW. No adverse effect was observed.

In healthy volunteers given single 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:** L04AC07

### 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

Two dosage 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. Eighty-three percent 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).

### Systemic juvenile idiopathic arthritis

In a 12-week double-blind, placebo-controlled study, patients received either 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

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 $C_{min}$.

**Distribution**

The volume of distribution at steady state is 6.4 l.

**Elimination**

Clearance is concentration-dependent but not dose-proportional. Linear clearance is estimated at 12.5 ml/h. Non-linear clearance plays a major role at low concentrations. Once non-linear clearance is saturated at higher tocilizumab concentrations, clearance is mainly determined by linear clearance.
The elimination half-life ($t_{½}$) of tocilizumab is concentration-dependent. The concentration-dependent apparent $t_{½}$ at steady state is 11 days for 4 mg/kg and 13 days for 8 mg/kg every 4 weeks.

**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 other forms of JIA*

The pharmacokinetics of tocilizumab were studied in clinical trials conducted in pediatric patients with idiopathic juvenile arthritis. In children over 7 years of age and adolescents, pharmacokinetic parameters after intravenous administration of 8 mg/kg every 2 or 4 weeks were similar to those in adults. Systemic clearance ranged from 0.2 to 0.3 ml/h/kg, and half-life was 4–6 days. Insufficient data are available for children under 7 years of age.

## 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 embryofetal development. However, a slight increase in abortion/embryofetal 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.

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

## Additional remarks

### Incompatibilities

Actemra must not be mixed with other medicinal products apart from the sterile 0.9% sodium chloride solution mentioned in *Instructions for preparation*. No incompatibility

has been found between Actemra and infusion bags and sets made of polyvinyl chloride, polyethylene or polypropylene.

### Stability

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

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.

### Special storage instructions

Store at 2–8°C (in the refrigerator).

Do not freeze.

Store the vial in its original pack, protected from light.

### Instructions for preparation

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

1) Under aseptic conditions, using a disposable syringe, withdraw the requisite quantity of Actemra (0.4 ml/kg BW or 0.6 ml/kg in SJIA patients weighing less than 30 kg) from one or more unopened vials. Discard any unused portion left in a vial.
2) Using another disposable syringe, withdraw and discard the same quantity as that of the Actemra from a 100 ml infusion bag (for patients weighing ≥30 kg) or a 50 ml infusion bag (for SJIA patients weighing less than 30 kg) containing pyrogen-free 0.9% (w/v) sodium chloride solution.
3) Still under aseptic conditions, inject the volume of Actemra previously withdrawn from the vial(s) into the 100 ml or 50 ml infusion bag. The resulting preparation now contains the originally withdrawn quantity of tocilizumab 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 perfusion) 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.

## Packs

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

Medicine: keep out of reach of children

Current at January 2015

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