PROFESSIONAL INFORMATION LEAFLET

SCHEDULING STATUS

S4

1 NAME OF MEDICINE

Actemra® 80 Infusion (Parenteral)

Actemra ® 200 Infusion (Parenteral)

Actemra ® 400 Infusion (Parenteral)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: tocilizumab

Each single use vial contains 20 mg tocilizumab/mL

ACTEMRA 80 contains 80 mg tocilizumab in 4 mL

ACTEMRA 200 contains 200 mg tocilizumab in 10 mL

ACTEMRA 400 contains 400 mg tocilizumab in 20 mL

Excipients with known effect: Sucrose

Contains sugar: (80 mg contains 200.00 mg, 200 mg contains 500.00 mg and 400 mg contains 1, 000.00 mg of sucrose). (See section 4.4).

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

A clear to opalescent, colourless to pale yellow solution.

CLINICAL PARTICULARS

4.1 Therapeutic indication

Rheumatoid Arthritis (RA)

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

- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate (MTX).
- the treatment of moderate to severe active rheumatoid arthritis in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

In these patients, Actemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Actemra has been shown to reduce the rate of progression of joint damage as measured by modified total Sharp-Genant radiographic score and to improve physical function when given in combination with MTX.

Polyarticular Juvenile Idiopathic Arthritis (pJIA)

Actemra, in combination with MTX, is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older. Actemra can be given alone in patients intolerant to MTX or where the treatment response with MTX is inadequate.

Systemic Juvenile Idiopathic Arthritis (sJIA)

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

4.2 Posology and method of administration

Method of Administration

Treatment should be initiated by medical practitioners experienced in the diagnosis and treatment of RA, pJIA or sJIA.

Rheumatoid Arthritis (RA)

The recommended dose of Actemra for adult patients is 8 mg/kg body weight, given once every four weeks as an IV infusion over one hour.

For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended. See *Pharmacokinetic properties*.

Doses above 1,2 g have not been evaluated in clinical studies.

Dose adjustments due to laboratory abnormalities. *See* section 4.4

- Liver enzyme abnormalities

Laboratory value	Action
> 1 to 3x Upper Limit of Normal (ULN)	Dose modify concomitant MTX if appropriate. For persistent increases in this range, reduce Actemra dose to 4 mg/kg or interrupt Actemra until alanine aminotransferase (ALT) or aspartate aminotransferase (AST) have normalised. Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate.

> 3 to 5x ULN (confirmed by repeat testing. See section 4.4)	Interrupt Actemra dosing until < 3x ULN. When values reach < 3x ULN, resume Actemra at 4 mg/kg or 8 mg/kg dose. For persistent increases > 3x ULN, discontinue Actemra.
> 5x ULN	Discontinue Actemra.

- Low absolute neutrophil count (ANC)

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

Laboratory value (cells x 10^9/ℓ)	Action
ANC > 1	Maintain dose.
ANC 0,5 to 1	Interrupt Actemra dosing. When ANC increases > 1 x 10^9/ℓ resume Actemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate.
ANC < 0,5	Discontinue Actemra.

- Low platelet count

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

Polyarticular Juvenile Idiopathic Arthritis (pJIA)

The recommended dose of Actemra for patients with pJIA is:

- 10 mg/kg once every four weeks for patients weighing < 30 kilograms (kg) as an IV infusion.
- 8 mg/kg once every four weeks for patients weighing ≥ 30 kg as an IV infusion.

A change in dose should only be based on a consistent change in the patient's body weight over time. Actemra can be used alone or in combination with MTX.

Systemic Juvenile Idiopathic Arthritis (sJIA)

The recommended dose of Actemra for patients with sJIA is:

- 12 mg/kg once every two weeks in patients weighing < 30 kg as an IV infusion.
- 8 mg/kg once every two weeks in patients weighing ≥ 30 kg as an IV infusion.

The dose should be calculated on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time.

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

- Liver enzyme abnormalities

Laboratory value	**Action**
> 1 to 3x ULN	Dose modify concomitant MTX if appropriate.

	For persistent increases in this range, interrupt Actemra until ALT/AST have normalised.
> 3x ULN to 5x ULN	Dose modify concomitant MTX if appropriate. Interrupt Actemra dosing until < 3x ULN and follow the recommendations above for > 1 to 3x ULN.
> 5x ULN	Discontinue Actemra. The decision to discontinue Actemra in pJIA or sJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low absolute neutrophil count (ANC)

Laboratory value (cells x 10^9/ℓ)	**Action**
ANC > 1	Maintain dose.
ANC 0,5 to 1	Interrupt Actemra dosing. When ANC increases > 1 x 10^9/ℓ resume Actemra
ANC < 0,5	Discontinue Actemra. The decision to discontinue Actemra in pJIA or sJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

- Low platelet count

Laboratory value (cells x 10^3/µℓ)	**Action**
50 to 100	Dose modify MTX if appropriate.

	Interrupt Actemra dosing. When platelet count is > 100 x 10^3/µℓ resume Actemra.
< 50	Discontinue Actemra. The decision to discontinue Actemra in pJIA or sJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

Available data suggest that clinical improvement is observed within 6 weeks for sJIA patients or 12 weeks for pJIA patients following initiation of treatment with Actemra. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe. Reduction of Actemra dose due to laboratory abnormalities has not been studied in pJIA or sJIA patients.

Special populations

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

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

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. See *Pharmacokinetic Properties*. Renal function should be monitored closely in these patients.

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

Method of administration

After dilution, Actemra for RA, pJIA and sJIA patients should be administered as an intravenous infusion over 1 hour. pJIA and sJIA patients ≥ 30 kg and RA patients: Actemra should be diluted to a final volume of 100 mℓ with sterile, apyrogenic sodium chloride 9 mg/mℓ (0,9 %) solution for injection using aseptic technique. pJIA and sJIA patients < 30 kg: Actemra should be diluted to a final volume

of 50 mℓ with sterile, apyrogenic sodium chloride 9 mg/mℓ (0,9 %) solution for injection using aseptic technique.

Special precautions for disposal and other handling:

Instructions for dilution prior to administration:

Parenteral medicinal products should be inspected visually for particulate matter or discolouration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted.

pJIA or *sJIA patients ≥ 30 kg and RA patients*

Under aseptic conditions, withdraw a volume of sterile, apyrogenic sodium chloride 9 mg/mℓ (0,9 %) solution for injection, equivalent to the volume of Actemra concentrate required for the patient's dose, from the 100 mℓ infusion bag. Discard this sodium chloride solution. Under aseptic conditions, withdraw the required amount of Actemra concentrate (**0,4 mℓ/kg**) from the vial/s and introduce into the 100 mℓ infusion bag. This results in a final volume of 100 mℓ. To mix the solution, gently invert the bag to avoid foaming.

pJIA patients < 30 kg

Under aseptic conditions, withdraw a volume of sterile, apyrogenic sodium chloride 9 mg/mℓ (0,9 %) solution for injection, equivalent to the volume of Actemra concentrate required for the patient's dose, from the 50 mℓ infusion bag. Discard this sodium chloride solution. Under aseptic conditions, withdraw the required amount of Actemra concentrate equal to **0,5 mℓ/kg** of the patient's body weight from the Actemra vial/s and introduce into the 50 mℓ infusion bag. This results in a final volume of 50 mℓ. To mix the solution, gently invert the bag to avoid foaming.

sJIA patients < 30 kg

Under aseptic conditions, withdraw a volume of sterile, apyrogenic sodium chloride 9 mg/mℓ (0,9 %) solution for injection, equivalent to the volume of Actemra concentrate required for the patient's dose, from the 50 mℓ infusion bag. Discard this sodium chloride solution. Under aseptic conditions, withdraw the required amount of Actemra concentrate equal to **0,6 mℓ/kg** of the patient's body weight from the vial/s and introduce into the 50 mℓ infusion bag. This results in a final volume of 50 mℓ. To mix the solution, gently invert the bag to avoid foaming. Actemra is for single use only.

4.3 Contraindications

Hypersensitivity to the tocilizumab or to any of the excipients. Active, severe infections. See section 4.4

4.4 Special warnings and precautions for use

Infections

Serious and sometimes fatal infections have been reported in patients receiving Actemra. See section 4.8.

Actemra treatment should not be initiated in patients with active infections. Administration of Actemra should be interrupted if a patient develops a serious infection until the infection is controlled. See section 4.3 and S4.8. Medical practitioners should exercise caution when considering the use of Actemra in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes) which may predispose patients to infections.

Vigilance for the timely detection of serious infection is recommended for patients receiving biological treatments for moderate to severe RA, pJIA or sJIA as signs and symptoms of acute inflammation may be lessened, associated with suppression of the acute phase reactants. The effects of Actemra on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered

when evaluating a patient for a potential infection. Patients (including RA and younger children with pJIA or sJIA who may be less able to communicate their symptoms) and parents/guardians of pJIA or sJIA patients should be instructed to contact their medical practitioner immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

Tuberculosis

RA, pJIA and sJIA patients should be screened for latent tuberculosis (TB) infection prior to starting Actemra therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating Actemra.

Complications of diverticulitis

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

Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylaxis have been reported in association with infusion of Actemra. In the post marketing setting, events of serious hypersensitivity and anaphylaxis have occurred in patients treated with a range of doses of Actemra, with or without concomitant arthritis therapies, premedication, and/or a previous hypersensitivity reaction. In the post marketing setting, cases with a fatal outcome have been reported with intravenous Actemra. These events have occurred as early as the first infusion of Actemra, see section 4.3 and 4.8.

Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during administration of Actemra. If an anaphylactic reaction or other serious hypersensitivity/serious infusion related reaction occurs, administration of Actemra should be stopped immediately and Actemra should be permanently discontinued.

Active hepatic disease and hepatic impairment

Treatment with Actemra, particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases. See section 4.8. Therefore, caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment, as the safety of Actemra in these patients has not been adequately studied. See *Special Dosage Instructions*.

Hepatic transaminase elevations

In clinical trials, transient or intermittent mild and moderate elevations of hepatic transaminases have been observed with Actemra treatment, without progression to hepatic injury. See section 4.8. An increased frequency of these elevations was observed when potentially hepatotoxic medicines (e.g. MTX) were used in combination with Actemra.

Caution should be exercised when considering initiation of Actemra treatment in patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1,5x upper limit of normal (ULN). In patients with baseline ALT or AST > 5x ULN, treatment is not recommended.
ALT and AST levels should be monitored in RA patients every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended modifications based on transaminases see section 4.2. For ALT or AST elevations > 3 - 5x ULN, confirmed by repeat testing, Actemra treatment should be interrupted. Once the patient's hepatic transaminases are below 3x ULN, treatment with Actemra may recommence at 4 or 8 mg/kg.

In pJIA and sJIA patients, ALT and AST levels should be monitored at the time of the second infusion and thereafter according to good clinical practice. See section 4.2

Neutropenia

Decreases in neutrophil counts have occurred following treatment with Actemra 8 mg/kg in combination with MTX. See section 4.8. There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist.

Caution should be exercised when considering initiation of Actemra treatment in patients with a low absolute neutrophil count (ANC) < 2 x 10^9/ℓ. In patients with an ANC < 0,5 x 10^9/ℓ, treatment is not recommended.

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

Neutrophils should be monitored in RA 4 to 8 weeks after start of therapy and thereafter according to good clinical practice. For recommended dose modifications based on ANC counts, see section 4.2.

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

Thrombocytopenia

Treatment with Actemra was associated with a reduction in platelet counts. Treatment-related reduction in platelets was not associated with serious bleeding events in clinical trials. See section 4.8.

Caution should be exercised when considering initiation of Actemra treatment in patients with a platelet count below 100 x 10^3/µℓ. In patients with a platelet count < 50 x 10^3/µℓ, treatment is not recommended.

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

In pJIA and sJIA: Platelets should be monitored at the time of the second infusion and thereafter, according to good clinical practice. See section 4.2

Lipid parameters

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

Assessment of lipid parameters should be performed in RA, pJIA and sJIA patients 4 to 8 weeks following initiation of Actemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia. The long term effect of the raised lipids is still unknown.

Demyelinating disorders

Medical practitioners should be vigilant for symptoms potentially indicative of new-onset central demyelinating disorders. The potential for central demyelination with Actemra is currently unknown.

Malignancy

The risk of malignancy is increased in patients with RA. Immunomodulatory medicines, such as Actemra may increase the risk of malignancy.

Vaccinations

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

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

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

It is recommended that all patients, particularly pJIA and sJIA patients, be brought up to date with all immunisations in agreement with current immunisation guidelines, prior to initiating Actemra therapy. The interval between live vaccinations and initiation of Actemra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

Viral Reactivation

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

Cardiovascular risk

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

Macrophage activation syndrome (MAS)

In sJIA: MAS is a serious life-threatening disorder that may develop in patients with sJIA. In clinical trials, Actemra has not been studied in patients during an episode of active MAS.

Sodium

Actemra contains 1,17 mmol (or 26,55 mg) sodium per maximum dose of 1 200 mg. Information to be taken into consideration by patients on a controlled sodium diet. Doses below 1 025 mg of Actemra contain less than 1 mmol sodium (23 mg), i.e. essentially “sodium free”.

Sugar

Actemra contains sucrose. Patients with the rare hereditary conditions of galactose intolerance lactase deficiency, glucose-galactose malabsorption intolerance should not take Actemra

Actemra contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Concomitant administration of a single dose of 10 mg/kg Actemra with 10 - 25 mg MTX once weekly had no clinically significant effect on MTX exposure.

Population pharmacokinetic analysis did not detect any effect of MTX, non-steroidal anti-inflammatory drugs and corticosteroids on Actemra clearance.

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

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

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

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

When starting or stopping therapy with Actemra, patients taking medicinal products which are individually dose-adjusted and are metabolised via CYP450 3A4, 1A2, or 2C9 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin or benzodiazepines) should be monitored as doses may need to be increased to maintain therapeutic effect. Given its long elimination half-life ($t_{½}$), the effect of Actemra on CYP450 enzyme activity may persist for several weeks after stopping therapy.

Combination with TNF antagonists

There is no experience with the use of Actemra in combination with TNF antagonists or other biological treatments for RA or sJIA patients. Actemra is not recommended for use with other biological agents.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy has not been established.

Pregnancy

A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose.

Actemra should not be used in pregnancy

Breastfeeding/Lactation

Lactation

It is unknown whether ACTEMRA is excreted in human breast milk. The excretion of Actemra in milk has not been studied in animals.

Breastfeeding should be discontinued during treatment with Actemra.

4.7 Effects on ability to drive and use machines.

No studies on the effects on the ability to drive and use machines have been performed. However, given that dizziness has been commonly reported, patients who experience this adverse reaction should be advised not to drive or use machines until it has resolved.

4.8 Undesirable effects

Clinical Trials

Rheumatoid Arthritis (RA)

A total of 3 778 patients received at least one dose of Actemra 4 mg/kg or 8 mg/kg**.**

The adverse drug reactions (ADRs) presented in Table 1 are based on the safety of Actemra studied in 4 placebo-controlled studies (Studies II, III, IV and V) and 1 MTX-controlled study (Study I).

The control period in 4 of the studies was 6 months and in 1 study was up to 2 years. In these studies 774 patients received Actemra 4 mg/kg in combination with MTX, 1 870 patients received Actemra 8 mg/kg in combination with MTX or other DMARDs and 288 patients received Actemra 8 mg/kg monotherapy.

The long-term exposure population includes all patients who received at least one dose of Actemra either in the double-blind control period or open-label extension phase in studies. Of the 4 009

patients in this population, 3 577 received treatment for at least 6 months, 3 296 for at least one year; 2 806 received treatment for at least two years and 1 222 for three years.

The most commonly reported ADRs (occurring in ≥ 5 % of patients treated with Actemra monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

The ADRs listed in Table 1 are presented by system organ class and frequency categories, defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10) or uncommon (≥ 1/1 000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. Summary of ADRs occurring in patients with RA receiving Actemra as monotherapy or in combination with MTX or other DMARDs in the double-blind controlled period.

System Organ Class	**Very Common**	**Common**	**Uncommon**
Infections and infestations	Upper respiratory tract infections	Cellulitis, pneumonia, oral herpes simplex, herpes zoster	Diverticulitis
Gastrointestinal disorders		Abdominal pain, mouth ulceration, gastritis	Stomatitis, gastric ulcer
Skin and subcutaneous tissue disorders		Rash, pruritus, urticaria	

Nervous system disorders		Headache, dizziness	
Investigations		Increased hepatic transaminases, increased weight, increased total bilirubin*	
Vascular disorders		Hypertension	
Blood and lymphatic system disorders		Leucopenia, neutropenia	
Metabolism and nutrition disorders	Hypercholesterolaemia*		Hypertriglyceridaemia
General disorders and administration site conditions		Peripheral oedema, hypersensitivity reactions	
Eye disorders		Conjunctivitis	
Respiratory, thoracic and mediastinal disorders		Cough, dyspnoea	
Renal disorders			Nephrolithiasis
Endocrine disorders			Hypothyroidism

* Includes elevations collected as part of routine laboratory monitoring (see text below)

Infections:

In the controlled studies the rate of all infections reported with Actemra 8 mg/kg plus DMARD treatment was 127 events per 100 patient-years compared to 112 events per 100 patient-years in the placebo plus DMARD group. In the long-term exposure population the overall rate of infections with Actemra was 108 events per 100 patient-years exposure.

In controlled clinical studies, the rate of serious infections with Actemra 8 mg/kg plus DMARDs was 5,3 events per 100 patient-years exposure compared to 3,9 events per 100 patient-years exposure in the placebo plus DMARD group. In the monotherapy study the rate of serious infections was 3,6 events per 100 patient-years of exposure in the Actemra group and 1,5 events per 100 patient-years of exposure in the MTX group.

In the long-term safety population (core and extension studies) the rate of serious infections observed with Actemra plus DMARD treatment was 4,7 events per 100 patient-years exposure. Reported serious infections, some with fatal outcome, included active tuberculosis, which may present with intrapulmonary or extrapulmonary disease, invasive pulmonary infections, including candidiasis, aspergillosis, coccidiodomycosis and *pneumocystis jirovecii,* pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis.

Gastrointestinal (GI) perforation:

During the six month controlled clinical trials, the overall rate of GI perforation was 0,26 events per 100 patient-years with Actemra therapy. In the long-term exposure population the overall rate of GI perforation was 0,28 events per 100 patient-years. Reports of GI perforation on Actemra were primarily reported as complications of diverticulitis including generalised purulent peritonitis, lower gastrointestinal perforation, fistula and abscess.

Infusion reactions:

Adverse events associated with infusion (selected events occurring during or within 24 hours of infusion) were reported by 6,9 % of patients in the Actemra 8 mg/kg plus DMARD group and 5,1 % of patients in the placebo plus DMARD group. Events reported during the infusion were primarily episodes of hypertension; events reported within 24 hours of finishing an infusion were headache and skin reactions (rash, urticaria). These events were not treatment limiting.

The rate of anaphylactic reactions (occurring in a total of 6/3 778 patients, 0,2 %) was several-fold higher with the 4 mg/kg dose, compared to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with Actemra and requiring treatment discontinuation, were reported in a total of 13 out of 3 778 patients (0,3 %) treated with Actemra during the controlled and open-label clinical trials. These reactions were generally observed during the second to fifth infusions of Actemra. See section 4.4.

Immunogenicity:

A total of 2 876 patients have been tested for anti-tocilizumab antibodies in the controlled clinical trials. Of the 46 patients (1,6 %) who developed anti-tocilizumab antibodies, 6 had an associated medically significant hypersensitivity reaction, of which 5 led to permanent discontinuation of treatment. In 30 patients (1,1 %) who developed neutralising antibodies, no apparent correlation to clinical response was observed.

Early Rheumatoid Arthritis

Study VI1 (WA19926) evaluated 1 162 patients with early, moderate to severe RA who were naïve to treatment with both MTX and a biologic agent. The overall safety profile observed in the Actemra treatment groups was consistent with the known safety profile of Actemra (see Table 1).

Polyarticular Juvenile Idiopathic Arthritis

The safety of intravenous Actemra was studied in 188 paediatric patients, 2 to 17 years of age, with pJIA. The total patient exposure in the Actemra all exposure population was 184,4 patient years. In general, the types of adverse drug reactions in patients with pJIA were similar to those seen in RA and sJIA patients, see Table 1.

Infections

The rate of infections in the Actemra all exposure population was 163,7 per 100 patient years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was numerically higher in patients weighing < 30 kg treated with 10 mg/kg tocilizumab (12,2 per 100 patient years) compared to patients weighing ≥ 30 kg, treated with 8 mg/kg Actemra (4,0 per 100 patient years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing < 30 kg treated with 10 mg/kg Actemra (21,4 %) compared to patients weighing ≥ 30 kg, treated with 8 mg/kg Actemra (7,6 %).

Infusion Reactions

In pJIA patients, infusion related reactions are defined as all events occurring during or within 24 hours of an infusion. In the Actemra all exposure population, 11 patients (5,9 %) experienced infusion reactions during the infusion, and 38 patients (20,2 %) experienced an event within 24 hours of an infusion. The most common events occurring during infusion were headache, nausea and hypotension and within 24 hours of infusion were dizziness and hypotension. In general, the adverse drug reactions observed during or within 24 hours of an infusion were similar in nature to those seen in RA and sJIA patients.

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

Immunogenicity

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

Systemic Juvenile Idiopathic Arthritis

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

In general, the adverse drug reactions in patients with sJIA were similar in type to those seen in RA patients.

Infections:

In the 12 week controlled trial the rate of all infections in the Actemra group was 344,7 per 100 patient-years and 287,0 per 100 patient-years in the placebo group. In the on-going open-label extension study (Part II) the overall rate of infections remained similar at 306,6 per 100 patient-years. In the 12 week controlled trial, the rate of serious infections in the Actemra group was 11,5 per 100 patient-years. In the on-going open-label extension study the overall rate of serious infection remained stable at 11,3 per 100 patient-years. Reported serious infections were similar to those seen in RA patients with the addition of varicella and otitis media.

Infusion reactions:

For sJIA patients infusion related reactions are defined as all events occurring during or within 24 hours of an infusion. In the 12 week controlled trial, 4,0 % of patients from the Actemra group

experienced events occurring during infusion, one event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment.

In the 12 week controlled trial, 16 % of patients in the Actemra group and 5,4 % of patients in the placebo group experienced an event within 24 hours of infusion. In the Actemra group, the events included, but were not limited to rash, urticaria, diarrhoea, epigastric discomfort, arthralgia and headache. One of these events (urticaria) was considered serious.

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

Immunogenicity:

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

Haematological abnormalities

Neutrophils:

Rheumatoid Arthritis (RA):

Decreases in neutrophil counts below 1 x 10^9/ℓ occurred in 3,4 % of patients on Actemra 8 mg/kg plus DMARDs compared to < 0,1 % of patients on placebo plus DMARDs. Approximately half of the patients who developed an ANC < 1 x 10^9/ℓ did so within 8 weeks after starting therapy. Decreases below 0,5 x 10^9/ℓ were reported in 0,3 % patients receiving Actemra 8 mg/kg plus DMARDs. There was no clear association between decreases in neutrophils and the occurrence of serious infections.

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

Polyarticular Juvenile Idiopathic Arthritis (pJIA):

During routine laboratory monitoring in the Actemra all exposure 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 x 10^9/ℓ and the occurrence of serious infections.

Systemic Juvenile Idiopathic Arthritis (sJIA):

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

In the on-going open-label extension study decreases in neutrophil counts below 1 x 10^9/ℓ, occurred in 15 % of the Actemra group. There was no clear relationship between decreases in neutrophils below 1 x 10^9/ℓ and the occurrence of serious infections.

Platelets:

Rheumatoid Arthritis (RA):

Decreases in platelet counts below 100 x 10^3/µℓ occurred in 1,7 % of patients on Actemra 8 mg/kg plus DMARDs compared to < 1 % on placebo plus DMARDs. These decreases occurred without associated bleeding events.

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

Polyarticular Juvenile Idiopathic Arthritis (pJIA):

During routine laboratory monitoring in the Actemra all exposure population, 1 % of patients had a decrease in platelet count to ≤ 50 × 10^3/µℓ without associated bleeding events.

Systemic Idiopathic Juvenile Arthritis (sJIA):

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

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

Hepatic transaminase elevations:

Rheumatoid Arthritis (RA):

Transient elevations in ALT/AST > 3 x ULN were observed in 2,1 % of patients on Actemra 8 mg/kg compared to 4,9 % of patients on MTX and in 6,5 % of patients who received 8 mg/kg Actemra plus DMARDs compared to 1,5 % of patients on placebo plus DMARDs. The addition of potentially hepatotoxic medicines (e.g. MTX) to Actemra monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST > 5 x ULN were observed in 0,7 % of Actemra monotherapy patients and 1,4 % of Actemra plus DMARD patients, the majority of whom were discontinued from Actemra treatment. These elevations were not associated with clinically relevant increase in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic impairment. During the double-blind controlled period, the incidence of indirect bilirubin greater than the upper limit of normal, collected as a routine laboratory parameter, was 6,2 % in patients treated with Actemra 8 mg/kg plus DMARD. A total of 5,8 % of patients experienced an elevation of indirect bilirubin of > 1 to 2 x ULN and 0,4 % had an elevation of > 2 x ULN.

During the double-blind controlled period and with long-term exposure population, the pattern and incidence of elevations in ALT/AST remained consistent with what was seen in the 6 month controlled clinical trials.

In Study VII, MTX-naïve adult patients with moderate to severe, active early RA (mean disease duration ≤ 6 months) experienced more transient elevations in ALT > 3 x ULN compared with the long-term/all control exposure population. This was observed in both Actemra treated patients and MTX monotherapy patients.

Polyarticular Juvenile Idiopathic Arthritis (pJIA):

During routine laboratory monitoring in the Actemra all exposure population, elevation in ALT or AST ≥ 3 x ULN occurred in 3,7 % and < 1 % of patients, respectively.

Systemic Juvenile Idiopathic Arthritis (sJIA):

During routine laboratory monitoring in the 12 week controlled trial, elevation in ALT or AST ≥ 3 x ULN occurred in 5 % and 3 % of patients, respectively, in the Actemra group, and in 0 % of the placebo group.

In the on-going open-label extension study, elevation in ALT or AST ≥ 3 x ULN occurred in 12 % and 4 % of patients, respectively, in the Actemra group.

Immunoglobulin G:

sJIA patients: IgG levels decrease during therapy. A decrease to the lower limit of normal occurred in 15 patients at some point in the study.

Lipid parameters:

Rheumatoid Arthritis (RA):

During the six month controlled trials, increases of lipid parameters such as total cholesterol, triglycerides, low density lipoprotein (LDL) cholesterol, and/or high density lipoprotein (HDL) cholesterol were observed. See section 4.4. Approximately 24 % of patients receiving Actemra in clinical trials experienced sustained elevations in total cholesterol > 6,2 mmol/ℓ, with 15 % experiencing a sustained increase in LDL to ≥ 4,1 mmol/ℓ. Elevations in lipid parameters responded to treatment with lipid-lowering agents.

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

Polyarticular Juvenile Idiopathic Arthritis (pJIA):

During routine laboratory monitoring in the Actemra long-term/all exposure population, elevation in total cholesterol > 1,5 - 2x ULN occurred in one patient (0,5 %) and elevation in LDL > 1,5 - 2x ULN in one patient (0,5 %).

Systemic Juvenile Idiopathic Arthritis (sJIA):

During routine laboratory monitoring in the 12 week controlled trial, elevation in total cholesterol > 1,5x ULN to 2 x ULN occurred in 1,5 % of the Actemra group and none in the placebo group. Elevation in LDL > 1,5x ULN to 2x ULN occurred in 1,9 % of patients in the Actemra group and 0 % of the placebo group.

In the on-going open-label extension study, the pattern and incidence of elevations in lipid parameters remained consistent with the 12 week controlled trial data.

Malignancies:

The clinical data are insufficient to assess the potential incidence of malignancy following exposure to Actemra. Long-term safety evaluations are on-going.

Post Marketing

The safety profile in post marketing experience is consistent with clinical trial data with the exception of a case of fatal anaphylactic reaction that has been reported during Actemra treatment in a RA patient. See section 4.4.

Stevens-Johnson Syndrome (SJS) has been reported during treatment with Actemra.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via he 6.04 Adverse Drug Reaction Report Form , found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There are limited data available on overdose with Actemra. Side effects reported with the use of Actemra may occur but the frequency and/or severity thereof may be different from those reported with therapeutic use. Treatment is palliative and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors; ATC code: L04AC07

Mechanism of Action

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

5.2 Pharmacokinetic properties

Rheumatoid Arthritis (RA)

The pharmacokinetics of tocilizumab were determined by using a population pharmacokinetic analysis on a database composed of 1 793 rheumatoid arthritis (RA) patients treated with a one-hour infusion of 4 and 8 mg/kg every 4 weeks for 24 weeks

The following parameters (predicted mean ± SD) were estimated for a dose of 8 mg/kg tocilizumab given every 4 weeks: steady-state area under curve (AUC) = 35 000 ± 15 500 h•µg/mℓ, trough concentration (Cmin) = 9,74 ± 10,5 µg/mℓ and maximum concentration (Cmax) = 183 ± 85,6 µg/mℓ and the accumulation ratios for AUC and Cmax were small, 1,22 and 1,06 respectively. The accumulation ratio was higher for Cmin (2,35), which was expected based on the non-linear clearance contribution at lower concentrations. Steady-state was reached following the first administration for Cmax, after 8 and 20 weeks for AUC and Cmin, respectively. Tocilizumab AUC, Cmin and Cmax increased with increase of body weight. At body weight ≥ 100 kg, the predicted mean (± SD) steady-state AUC, Cmin and Cmax 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 (AUC = 35 000 ± 15 500 h µg/mℓ, Cmin = 9,74 ± 10,5 µg/mℓ and Cmax = 183

± 85,6 µg/mℓ). The dose-response curve for tocilizumab flattens at higher exposure, resulting in smaller efficacy gains for each incremental increase in tocilizumab concentration such that clinically meaningful increases in efficacy were not demonstrated in patients treated with > 800 mg of tocilizumab. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended in patients ≥ 100 kg. See section 4.2.

Linearity

The pharmacokinetic parameters of tocilizumab did not change with time. A more than dose-proportional increase in the AUC and Cmin was observed for doses of 4 and 8 mg/kg every 4 weeks. Cmax increased dose-proportionally. At steady-state, predicted AUC and Cmin were 2,7 and 6,5 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively.

Polyarticular Juvenile Idiopathic Arthritis (pJIA)

The pharmacokinetics of tocilizumab was determined using a population pharmacokinetic analysis on a database composed of 188 patients with polyarticular juvenile idiopathic arthritis.

The following parameters are valid for a dose of 8 mg/kg tocilizumab (patients with a body weight (BW) ≥ 30 kg) given every 4 weeks. The predicted mean (□ SD) AUC4weeks, Cmax and Cmin of tocilizumab were 29 500 ± 8 660 µg•h/mℓ, 182 ± 37 µg/mℓ and 7,49 ± 8,2 µg/mℓ, respectively.

The following parameters are valid for a dose of 10 mg/kg tocilizumab (patients with a body weight < 30 kg) given every 4 weeks. The predicted mean (± SD) AUC4weeks, Cmax and Cmin of tocilizumab were 23 200 ± 6 100 µg•h/mℓ, 175 ± 32 µg/mℓ and 2,35± 3,59 µg/mℓ, respectively.

The accumulation ratios were 1,05 and 1,16 for AUC4weeks, and 1,43 and 2,22 for Cmin for 10 mg/kg (BW < 30 kg) and 8 mg/kg (BW ≥ 30 kg) doses, respectively. No accumulation for Cmax was observed.

Systemic Juvenile Idiopathic Arthritis (sJIA)

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 75 sJIA patients treated with 8 mg/kg (patients with a body weight of ≥ 30 kg) or 12 mg/kg (patients with a body weight < 30 kg) given every 2 weeks. The predicted mean (± SD) AUC2weeks, Cmax and Cmin of tocilizumab were 32 200 ± 9 960 µg·hr/mℓ, 245 ± 57,2 µg/mℓ and 57,5 ± 23,3 µg/mℓ respectively. The accumulation ratio for Cmin (week 12/week 2) was 3,2 ± 1,3. The tocilizumab Cmin was stabilised after week 12. Mean predicted tocilizumab exposure parameters were similar between the two body weight groups.

Distribution

In RA patients the central volume of distribution was 3,5 ℓ, the peripheral volume of distribution was 2,9 ℓ resulting in a volume of distribution at steady state of 6,4 ℓ.

In pJIA patients, the central volume of distribution was 1,98 ℓ (50 mℓ/kg), the peripheral volume of distribution was 2,1 ℓ (53 mℓ/kg), resulting in a volume of distribution at steady state of 4,08 ℓ (103 mℓ/kg).

In sJIA patients, the central volume of distribution was 0,94 ℓ, (35 mℓ/kg), the peripheral volume of distribution was 1,60 ℓ (60 mℓ/kg) resulting in a volume of distribution at steady state of 2,54 ℓ (95 mℓ/kg).

Elimination

Following intravenous administration, tocilizumab undergoes biphasic elimination from the circulation. The total clearance of tocilizumab was concentration-dependent and is the sum of the linear clearance and the non-linear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 12,5 mℓ/h in RA patients, 5,8 mℓ/h (0,146 mℓ/h/kg) in paediatric patients with pJIA and 7,1 mℓ/h (0,142 mℓ/h/kg) in sJIA patients. The concentration-dependent non-linear clearance plays a major role at low tocilizumab concentrations.

Once the non-linear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance. The t½ of tocilizumab was concentration-dependent in RA. At steady-state following a dose of 8 mg/kg every 4 weeks the effective t½ decreased with decreasing concentrations within a dosing interval from 14 days to 8 days.

The t1/2 of tocilizumab in children with pJIA is up to 16 days for the two body weight categories (8 mg/kg for body weight ≥ 30 kg or 10 mg/kg for body weight < 30 kg) during a dosing interval at steady state.

The t½ of tocilizumab in sJIA patients is up to 23 days for the two body weight categories (8 mg/kg for body weight ≥ 30 kg or 12 mg/kg for body weight < 30 kg) at week 12.

Special populations

Renal Impairment: No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab has been conducted. Most of the patients in the population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (creatinine clearance based on Cockcroft-Gault < 80 mℓ/min and ≥ 50 mℓ/min) did not impact on the pharmacokinetics of tocilizumab.

Hepatic impairment: No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab has been conducted.

Age, gender and ethnicity: Population pharmacokinetic analyses in adult rheumatoid arthritis patients showed that age, gender and ethnic origin did not affect the pharmacokinetics of tocilizumab.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients - disodium phosphate dodecahydrate, polysorbate 80, sodium dihydrogen phosphate dihydrate, sucrose and water for injections.

6.2 Incompatibilities

Not applicable

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road, Hertford Office Park,

Building E, Vorna Valley, Midrand,

Johannesburg, 1686

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Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER(S)

Actemra 80: 43/30.1/0944

Actemra 200: 43/30.1/0945

Actemra 400: 43/30.1/0946

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration: 4 March 2011

10. DATE OF REVISION OF THE TEXT

Last revision: 26 May 2023

Approved manufacturer(s):

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