PROFESSIONAL INFORMATION:

SCHEDULING STATUS

S4

1 NAME OF MEDICINE

Actemra® SC (Injection)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: tocilizumab

Each pre-filled syringe contains 162 mg tocilizumab in 0,9 mℓ.

Sugar free

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Colourless to slightly yellowish, clear to strongly opalescent liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indication Rheumatoid Arthritis (RA)

Actemra SC, 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 (RA) 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 SC can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Actemra SC 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.

Giant Cell Arteritis (GCA)

Actemra SC is indicated for the treatment of giant cell arteritis (GCA) in adult patients.

Polyarticular Juvenile Idiopathic Arthritis (pJIA)

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

Efficacy and safety of Actemra SC in children with a condition other than pJIA has not been established. Children below the age of two years have not been studied.

Systemic Juvenile Idiopathic Arthritis (sJIA)

Subcutaneous Formulation

Actemra is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 1 year of age and older.

Actemra SC can be given alone 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.

Actemra SC is administered with a single-use pre-filled syringe (PFS) with a needle safety device (NSD). The first few injections should be performed under the supervision of a qualified healthcare professional. The recommended injection sites (abdomen, thigh and upper arm) should be rotated and injections should never be given into moles, scars, or other areas where the skin is tender, bruised, red, hard or not intact.

Patients transitioning from Actemra IV therapy to SC administration should administer the first SC dose at the time of the next scheduled IV dose under the supervision of a qualified healthcare professional.

Actemra SC formulation is not intended for intravenous administration.

Assess suitability of patient or parent/guardian for SC home use and instruct patients or parent/guardian to inform a healthcare professional if they experience any symptoms of allergic reaction. Patients should seek immediate medical attention if they develop symptoms of serious allergic reactions (see WARNINGS AND SPECIAL PRECAUTIONS and SIDE EFFECTS).

Subcutaneous dosing regimen

Rheumatoid Arthritis (RA)

The recommended dose of Actemra SC for adult patients is 162 mg given once every week as a subcutaneous injection. Actemra SC can be used alone or in combination with MTX and/or other DMARDs.

Giant Cell Arteritis (GCA)

The recommended dose of Actemra SC for adult patients with GCA is 162 mg given once every week as a subcutaneous injection, in combination with a tapering course of glucocorticoids.

A dose of 162 mg given once every other week as a subcutaneous injection in combination with a tapering course of glucosteroids may be prescribed on clinical considerations.

Actemra SC can be used alone following discontinuation of glucocorticoids. In the event of patients experiencing a relapse of GCA during the course of Actemra SC therapy, the treating medical practitioner should consider re-introducing and/or escalating the dose of concomitant glucocorticoids (or restarting glucocorticoid therapy if it has been discontinued) according to best medical judgement/treatment guidelines.

Dose Modifications recommendations for RA and GCA

See WARNINGS AND SPECIAL PRECAUTIONS.

- **Liver enzyme abnormalities**

Laboratary Value	**Action**
> 1 to 3x ULN	Dose modify concomitant DMARDs (RA) or immunomodulatory agents (GCA) if appropriate. For patients on subcutaneous Actemra SC with persistent increases in this range, reduce Actemra SC injection frequency to every other week or interrupt Actemra SC until ALT/AST have normalized. Restart with weekly injection or injection every other week, as clinically appropriate.
> 3 to 5x ULN	Interrupt Actemra SC dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN For persistent increases > 3x ULN (confirmed by repeat testing, see section 2.4.4), discontinue Actemra SC
> 5x ULN	Discontinue Actemra SC

- Low absolute neutrophil count (ANC) [31]

In patients not previously treated with Actemra SC, 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 SC dosing. When ANC increases > 1 x 10^9/ℓ resume Actemra SC injection every other week and increase frequency to every week, as clinically appropriate.
ANC < 0,5	Discontinue Actemra SC.

- Low platelet count

Laboratory value (cells x 10^3/µℓ)	Action
50 to 100	Interrupt Actemra SC dosing. When platelet count is > 100 x 10^3/µℓ resume Actemra SC injection every other week and increase frequency to every week, as clinically appropriate.
< 50	Discontinue Actemra SC.

Polyarticular Juvenile Idiopathic Arthritis (pJIA)

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

The recommended dose of Actemra SC for patients with pJIA is:

- 162 mg once every three weeks for patients below 30 kg,
- 162 mg once every two weeks for patients ≥ 30 kg

Dose Modification Recommendations for pJIA:

Dose reduction of Actemra SC has not been studied in the pJIA or sJIA population. Dose interruptions of Actemra SC for laboratory abnormalities are recommended in patients with pJIA or sJIA and are similar to what is outlined above for patients with RA and GCA (also see WARNINGS AND SPECIAL PRECAUTIONS). If appropriate, concomitant methotrexate and/or other medications should be dose modified or stopped and Actemra SC dosing interrupted until the

clinical situation has been evaluated. In pJIA or sJIA the decision to discontinue Actemra SC for a laboratory abnormality should be based upon the medical assessment of the individual patient.

After proper training in injection technique, patients may self-inject Actemra SC if their doctor determines that it is appropriate and if the patient agrees to medical follow-up as necessary. The total content (0,9 mℓ) of the pre-filled syringe should be administered as a subcutaneous injection. The pre-filled syringe should not be shaken.
Comprehensive instructions for the administration of Actemra SC by the patient, using the pre-filled syringe, are given in the Patient Information Leaflet.

RA and GCA

Missed dose

If a patient misses a SC weekly injection of Actemra SC within 7 days of the scheduled dose, he/she should be instructed to administer the missed dose on the next scheduled day. If a patient misses a SC once every other week injection of Actemra SC within 7 days of the scheduled dose, he/she should be instructed to administer the dose immediately and the next dose on the next scheduled day.

Special dosing instructions

Children

The safety and efficacy of Actemra SC in children with conditions other than pJIA have not been established. Children below the age of two years have not been studied.
The safety and efficacy in patients aged less than 2 years in sJIA or less than 1 year with in sJIA have not been established.

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 or moderate renal impairment. Actemra SC has not been studied in patients with severe renal impairment (see *Pharmacokinetic Properties)*. Renal function should be monitored closely in these patients.

Hepatic Impairment

Actemra SC has not been studied in patients with hepatic impairment, and safety in patients with hepatic impairment has not been established. Therefore, no dose recommendations can be made.

Systemic Juvenile Idiopathic Arthritis (sJIA)

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

The recommended dose of Actemra SC for patients with sJIA is:

- 162 mg once every two weeks for patients below 30 kg,
- 162 mg once every week for patients ≥ 30 kg
- Patients between 1 year and 2 years of age must have a minimum body weight of 10 kg when receiving 162 mg SC tocilizumab

Dose Modification Recommendations for sJIA

Dose reduction of Actemra SC has not been studied in the sJIA population. Dose interruptions of Actemra SC for laboratory abnormalities are recommended in patients with sJIA and are similar to what is outlined above for patients with RA and GCA (also see WARNINGS AND SPECIAL PRECAUTIONS). If appropriate, concomitant methotrexate and/or other medications should be dose modified or stopped and Actemra SC dosing interrupted until the clinical situation has been evaluated. In sJIA, the decision to discontinue Actemra SC for a laboratory abnormality should be based upon the medical assessment of the individual patient.

4.3 Contraindications

- Actemra SC is contraindicated in patients with a known hypersensitivity to tocilizumab or to any of the excipients.
- Active, severe infections (see WARNINGS AND SPECIAL PRECAUTIONS).
- Active hepatic disease/hepatitis or a recent history of hepatic disease/hepatitis
- Impairment of hepatic/liver function (ALT and/or or AST) increases to ≥5x ULN before or during treatment.
    - Active or chronic hepatitis B
    - Concomitant use with other hepatotoxic medicines except methotrexate as approved under indications

4.4 Special warnings and precautions for use

Infections

Serious and sometimes fatal infections have been reported in patients receiving Actemra SC (see SIDE EFFECTS). Actemra SC treatment should not be initiated in patients with active infections. Administration of Actemra SC should be interrupted if a patient develops a serious infection until the infection is controlled (see CONTRAINDICATIONS and SIDE EFFECTS). Medical practitioners should exercise caution when considering the use of Actemra SC 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 timeous detection of serious infection is recommended for patients receiving immunosuppressive medicines such as Actemra SC as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute phase reactants. The effects of Actemra SC on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection.

Patients (which include younger children who may be less able to communicate their symptoms) and parents/guardians of minors, should be instructed to contact their medical practitioner

immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

Tuberculosis

All patients should be screened for active or latent tuberculosis (TB) infection prior to starting Actemra SC therapy. Patients with active or latent TB should be treated with standard anti-mycobacterial therapy before initiating Actemra SC.

Risks of tuberculosis disease

- An increased risk of tuberculosis (including disseminated and extra-pulmonary presentations) has been observed in patients treated with TNF-α inhibitors and similar immune-modulatory medicines.
- Tuberculosis in these patients may be due to reactivation of latent tuberculosis infection or due to new infections.
- Prophylactic treatment of a latent tuberculosis infection should be initiated prior to starting treatment with Actemra SC.
- Patients may become infected with tuberculosis during the course of therapy with Actemra SC and physicians should continue to monitor the patient for signs and symptoms of tuberculosis, including patients who have tested negative for latent tuberculosis at the start of therapy.

Treatment of tuberculosis should follow current national guidelines.

Complications of diverticulitis

Events of diverticular perforations have been reported with Actemra SC in patients treated with Actemra SC (see SIDE EFFECTS).

Actemra SC 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 Actemra SC. Such reactions may be more severe, and potentially fatal in patients who have experienced hypersensitivity reactions during previous administrations even if they have received premedication with steroids and antihistamines (see SIDE EFFECTS).

Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during administration of Actemra SC. If an anaphylactic reaction or other serious hypersensitivity/serious administration related reaction occurs, administration of Actemra SC should be stopped immediately and Actemra SC should be permanently discontinued (see DOSAGE AND DIRECTIONS FOR USE).

Active hepatic disease and hepatic impairment

Treatment with Actemra SC, particularly when administered concomitantly with
MTX, may be associated with elevations in hepatic transaminases (see SIDE EFFECTS).

Therefore, caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment, as the safety of Actemra SC in these patients has not been adequately studied (see DOSAGE AND DIERCTIONS FOR USE: *Special Dosage Instructions*).

Hepatotoxicity

Mild and moderate elevations of hepatic transaminases have been observed with Actemra SC treatment (see SIDE EFFECTS).

An increased frequency of these elevations was observed when potentially hepatotoxic medicines (e.g. MTX) were used in combination with Actemra SC.

Serious medicine-induced liver injury, including acute liver failure, hepatitis and jaundice, have been observed with Actemra SC (see SIDE EFFECTS, Post Marketing). Serious hepatic injury

occurred between 2 weeks to more than 5 years after initiation of Actemra SC. Cases of liver failure resulting in liver transplantation have been reported.

Caution should be exercised when considering initiation of Actemra SC treatment in patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above 1,5x upper limit of normal (ULN). In patients with baseline ALT or AST above 5x ULN, treatment is not recommended.

In RA, pJIA and GCA, ALT and AST should be monitored every 4 to 8 weeks for the first six months of treatment followed by every 12 weeks thereafter. For recommended dose modifications, including Actemra SC discontinuation based on transaminases levels see DOSAGE AND DIRECTIONS FOR USE.

Neutropenia

Treatment with Actemra SC was associated with neutropenia. Caution should be exercised when considering initiation of Actemra SC treatment in patients with a low absolute neutrophil count (ANC) below 2 x 10^9/ℓ. In patients with an ANC below 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 SC to date.

Neutrophils should be monitored in RA and GCA 4 to 8 weeks after start of therapy and thereafter according to good clinical practice. For recommended dose modifications based on ANC counts see DOSAGE AND DIRECTIONS FOR USE.

In pJIA and sJIA, neutrophils should be monitored at the time of the second administration and thereafter according to good clinical practice. For recommended dose modifications based on ANC counts see DOSAGE AND DIRECTIONS FOR USE.

Thrombocytopenia

Treatment with Actemra SC was associated with a reduction in platelet counts. Treatment-related reduction in platelets was not associated with serious bleeding events in clinical trials (see SIDE EFFECTS).

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

In RA and GCA, platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to good clinical practice. For recommended dose modifications based on ANC and platelet counts see DOSAGE AND DIRECTIONS FOR USE.

In pJIA and sJIA, platelets should be monitored at the time of the second administration and thereafter according to good clinical practice (see DOSAGE AND DIRECTIONS FOR USE).

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 SC (see SIDE EFFECTS).

Assessment of lipid parameters should be performed in patients treated with Actemra SC, 4 to 8 weeks following initiation of Actemra SC 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.

Systemic Juvenile Idiopathic Arthritis

Macrophage activation syndrome (MAS)

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

Demyelinating disorders

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

Malignancy

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

Vaccinations

Live and live attenuated vaccines should not be given concurrently with Actemra SC 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 SC.

In a randomised open-label study, adult RA patients treated with Actemra SC and methotrexate (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 paediatric or elderly patients, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Actemra SC therapy. The interval between live vaccinations and initiation of Actemra SC therapy should be in accordance with current vaccination guidelines regarding immunosuppressive medicines.

Viral Reactivation

Viral reactivation (e.g. hepatitis B virus) has been reported with biologic therapies for RA. In clinical studies with Actemra SC, 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

Transition from IV to SC therapy

Patients transitioning from Actemra IV therapy to SC administration should administer the first SC dose at the time of the next scheduled IV dose under the supervision of a qualified healthcare professional.

Actemra SC formulation is not intended for intravenous administration.

Medical practitioners should assess suitability of patient or parent/guardian for SC home use and instruct patients or parent/guardian to inform a healthcare professional if they experience symptoms of allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions (see DOSAGE AND DIRECTIONS FOR USE).

4.5 Interaction with other medicines and other forms of interaction

Infections

Interaction studies were only performed as per treatment of tocilizumab using the IV formulation. Concomitant administration of a single dose of 10 mg/kg tocilizumab with 10 - 25 mg MTX once weekly had no clinically significant effect on MTX exposure.

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

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

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

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

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

When starting or stopping therapy with tocilizumab, patients taking medicines which are individually adjusted and are metabolised via CYP450 3A4, 1A2, 2C9 or 2C19 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin or benzodiazepines) should be monitored as doses may need to be adjusted to maintain therapeutic effect. Given its long elimination half-life ($t_{½}$), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

Combination with TNF antagonists

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

4.6 Fertility, pregnancy and lactation

Pregnancy

A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose. There are no adequate data from the use of Actemra in pregnant women.

Breastfeeding/Lactation

It is unknown whether Actemra SC is excreted in human breast milk. The excretion of Actemra SC in milk has not been studied in animals. Breastfeeding should be discontinued during treatment with Actemra SC.

Fertility

No available data suggest an effect on fertility under treatment of 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 the dizziness has resolved.

4.8 Undesirable effects

Clinical Trials

The safety profile in this section comes from 4 510 patients exposed to Actemra IV and SC in clinical trials; the majority of these patients were participating in RA studies (n= 4 009), while the remaining

experience comes from pJIA (n=240), sJIA (n=112), and GCA (n=149) studies. The safety profile of Actemra across these indications remains similar and undifferentiated.

ADRs are listed according to clinical importance to the patient. Frequencies are defined as very common (≥1/10), common (≥1/100 to < 1/10) or uncommon (≥1/1000 to < 1/100), rare (≥ 1/10 000, < 1/1 000), very rare (< 1/10 000), including isolated reports. Within each frequency grouping, side effects are presented in order of decreasing seriousness.

Table 3: Summary of ADRs occurring in patients treated with Actemra

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 billirubin	
Vascular disorders		Hypertension	
Blood and lymphatic system disorders		Leucopenia, neutropenia	

System Organ Class	Very Common	Common	Uncommon
Metabolism and nutrition disorders	Hypercholesterolaemia		Hypertriglyceridaemia
General disorders and administration site conditions	Injection site reactions, including erythema, pruritus, pain, haematoma	Peripheral oedema, hypersensitivity reactions	
Respiratory, thoracic and mediastinal disorders		Cough, dyspnoea	
Eye disorders		Conjunctivitis	
Renal disorders			Nephrolithiasis
Endocrine disorders			Hypothyroidism

Rheumatoid Arthritis (RA):

Patients treated with subcutaneous Actemra SC

The safety of subcutaneous Actemra SC in RA was studied in a double-blind, controlled, multicentre study clinical trial, SC-I. The study compared the efficacy and safety of Actemra SC 162 mg administered every week versus 8 mg/kg IV in subjects with adult RA. All patients in the study received background non-biologic DMARD(s). The safety and immunogenicity observed for Actemra SC was consistent with the known safety profile of IV tocilizumab and no new or

unexpected adverse drug reactions were observed, see Table 3. A higher frequency of injection site reactions were observed in the SC arms compared with placebo SC injections in the IV arms.

RA: Immunogenicity

A total of 625 patients treated with Actemra SC 162 mg weekly were tested for anti-tocilizumab antibodies in a 6-month controlled period. Five patients (0,8 %) developed positive anti-tocilizumab antibodies; of these, all developed neutralising anti-tocilizumab antibodies.

A total of 1 454 Actemra SC all exposure patients have been tested for anti-tocilizumab antibodies, thirteen patients (0,9 %) developed positive anti tocilizumab antibodies, and of these 12 patients (0,8 %) developed neutralising anti-tocilizumab antibodies.

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

Giant Cell Arteritis

The safety of subcutaneous Actemra has been studied in one Phase III study (WA28119) with 251 GCA patients. The total patient years duration in the Actemra SC all exposure population was 138,5 patient years during the 12-month double blind, placebo-controlled phase of the study. The overall safety profile observed in the Actemra SC treatment groups was consistent with the known safety profile of Actemra (see Table 3).

GCA: Infections

The rate of infection/serious infection events was balanced between the Actemra SC weekly group (200,2/9,7 events per 100 patient years) versus placebo plus 26 weeks prednisone taper (156,0/4,2 events per 100 patient years) and placebo plus 52 weeks taper (210,2/12,5 events per 100 patient years) groups.

Polyarticular Juvenile Idiopathic Arthritis

The safety profile of Actemra SC and IV was studied in 240 paediatric patients with pJIA. In Study WA19977, 188 patients (2 to 17 years of age) were treated with Actemra IV and in Study WA28117, 52 patients (1 to 17 years of age) were treated with Actemra SC. The total patient exposure to Actemra in the pJIA all exposure population was 184,4 patient years for Actemra IV and 50,4

patient years for Actemra SC. In general, the safety profile observed in patients with pJIA was consistent with the known safety profile of Actemra with the exception of injection site reactions (ISRs), see Table 3. A higher frequency of ISRs was experienced by pJIA patients following Actemra SC injections compared to adult RA patients.

pJIA: Infections

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

pJIA: Injection Site Reactions (ISRs)

A total of 28,8 % (15/52) pJIA patients experienced ISRs to Actemra SC. These ISRs occurred in 44 % of patients ≥ 30 kg compared to 14,8 % of patients below 30 kg. The most common ISRs were injection site erythema, swelling, haematoma, pain and pruritis. All ISRs reported were non-serious Grade 1 events, and none of the ISRs required patient withdrawal from treatment or dose interruption.

pJIA: Immunogenicity

Positive neutralising anti-tocilizumab antibodies have been detected in clinical studies. However, no clear association between antibody development and clinical response or adverse events was observed.

Systemic Juvenile Idiopathic Arthritis

The safety profile of Actemra SC in sJIA was studied in 163 paediatric patients. In Study WA18221 (12-week trial and long term extension), 112 patients (2 to 17 years of age) were treated with Actemra IV and in Study WA28118 (52-week trial), 51 patients (1 to 17 years of age) were treated with SC Actemra SC. In general, the adverse drug reactions in patients with sJIA were similar in type to those seen in RA patients (see SIDE EFFECTS).

sJIA Infections

In the 12 week controlled trial (Study WA18221), the rate of all infections in the IV tocilizumab group was 344.7 and 11.5 per 100 patient-years and 287.0 per 100 patient-years in the placebo group. In the open label extension study the overall rate of infections remained similar and remained stable at 11.3 at 306.6 per 100 patient- years. Reported serious infections were similar to those seen in RA patients with the addition of varicella and otitis media. The rate of infection in sJIA patients treated with SC tocilizumab was comparable to sJIA patients treated with IV tocilizumab

sJIA: Injection Site Reactions (ISRs)

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

sJIA: Immunogenicity

In Study WA18221, all 112 patients were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti-tocilizumab antibodies with one of these patients having a hypersensitivity reaction leading to withdrawal [56]. In Study WA28118, 46 of the 51 (90.2%) patients tested for anti-tocilizumab antibodies at baseline had at least one post-baseline screening assay result. No patient developed positive anti-tocilizumab antibodies post-baseline

Haematological abnormalities

Neutrophils

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

Rheumatoid Arthritis (RA)

SC administration

During routine laboratory monitoring in the Actemra SC 6-month controlled period of clinical trial SC-1, a decrease in neutrophil count below 1 x 10^9/ℓ occurred in 2,9 % of patients on Actemra SC 162 mg weekly.

Giant Cell Arteritis (GCA)

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

Polyarticular Juvenile Idiopathic Arthritis (pJIA)

During routine laboratory monitoring in the Actemra IV all exposure population, a decrease in neutrophil count below 1 × 10^9/ℓ occurred in 3,7 % of patients treated with Actemra IV and 15,4 % of patients treated with Actemra SC.

Systemic Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the 12-week controlled trial (Study WA18221), a decrease in neutrophil counts below 1 × 109/L occurred in 7% of patients in the Actemra IV group, and in none in the placebo group. In the open-label extension study (WA18221), decreases in neutrophil counts below 1 x 109/L, occurred in 15% of the Actemra IV group. In the 52-week open-label trial (Study WA28118), neutrophil count decrease below 1 × 109/L occurred in 23.5% of patients treated with Actemra SC.

Platelets

Rheumatoid Arthritis (RA)

SC administration

During routine laboratory monitoring in the Actemra SC 6-month controlled period of clinical trial SC-1, none of the patients had a decrease in platelet count to ≤ 50 x 10^3/µℓ.

Giant Cell Arteritis

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

Polyarticular Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the Actemra IV all exposure population, a decrease in platelet count to ≤ 50 × 10^3/µℓ occurred in 1 % patients treated with Actemra IV, without associated bleeding events and in no patients treated with Actemra SC.

Systemic Juvenile Idiopathic Arthritis

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

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

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

Liver transaminase elevations

Rheumatoid Arthritis (RA)

SC administration

During routine laboratory monitoring in the Actemra SC 6-month controlled period of clinical trial SC-1, elevation in ALT or AST ≥ 3 x ULN occurred in 6,5 % and 1,4 % of patients, respectively on SC weekly.

Giant Cell Arteritis

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

Polyarticular Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the tocilizumab all exposure population, elevation in ALT or AST ≥ 3 x ULN occurred in 3,7 % and below 1 % of patients treated with Actemra IV, and in 9,6 % and 3,8 % patients treated with Actemra SC, respectively.

Polyarticular Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the tocilizumab all exposure population, elevation in ALT or AST ≥ 3 x ULN occurred in 3,7 % and below 1 % of patients treated with Actemra IV, and in 9,6 % and 3,8 % patients treated with Actemra SC, respectively.

Systemic Juvenile Idiopathic Arthritis

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

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

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

Elevations in lipid parameters

Rheumatoid Arthritis (RA)

SC administration

During routine laboratory monitoring in the Actemra SC 6-month controlled period of clinical trial SC-1, 19 % of patients on Actemra SC weekly experienced sustained elevations in total cholesterol above 6,2 mmol/ℓ (240 mg/dℓ) with 9 % experiencing a sustained increase in LDL to ≥ 4,1 mmol/ℓ (160 mg/dℓ) on Actemra SC weekly.

Giant Cell Arteritis

During routine laboratory monitoring in the Actemra SC 12-month double blind, placebo-controlled phase of study WA28119, 29 % of patients experienced elevations in total cholesterol above 6,2 mmol/ℓ (240 mg/dℓ), with 12 % experiencing an increase in LDL to ≥ 4,1 mmol/ℓ (160 mg/dℓ) in the Actemra SC weekly group.

Polyarticular Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the Actemra IV Study WA19977, 3,4 % and 10,4 % of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dℓ and total cholesterol value to ≥ 200 mg/dℓ at any time during the study treatment, respectively. In the Actemra SC study WA28117, 14,3 % and 12,8 % of patients experienced a post-baseline elevation

of their LDL-cholesterol value to ≥ 130 mg/dℓ and total cholesterol value to ≥ 200 mg/dℓ at any time during study treatment, respectively.

Systemic Juvenile Idiopathic Arthritis

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

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

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

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

Patients treated with Intravenous Actemra

Clinical Trials

Rheumatoid Arthritis (RA):

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

Infections

In the controlled studies the rate of all infections reported with Actemra IV 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 IV 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 IV 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 IV 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. Cases of opportunistic infections have also been reported.

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 IV 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 IV were primarily reported as complications of diverticulitis including generalised purulent peritonitis, lower gastrointestinal perforation, fistula and abscess.

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.

Haematological abnormalities

Neutrophils

IV administration

Decreases in neutrophil counts below 1 x 10^9/ℓ occurred in 3,4 % of patients on Actemra IV 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 IV 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.

Platelets

IV administration

Decreases in platelet counts below 100 x 10^3/µℓ occurred in 1,7 % of patients on Actemra IV 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.

Liver transaminase elevations

IV administration

Transient elevations in ALT/AST > 3x ULN were observed in 2,1 % of patients on Actemra IV 8 mg/kg compared to 4,9 % of patients on MTX and in 6,5 % of patients who received 8 mg/kg Actemra IV plus DMARDs compared to 1,5 % of patients on placebo plus DMARDs. The addition of potentially hepatotoxic medicines (e.g. MTX) to Actemra IV monotherapy resulted in increased frequency of these elevations.

Elevations of ALT/AST > 5x ULN were observed in 0,7 % of Actemra IV monotherapy patients and 1,4 % of Actemra IV plus DMARD patients, the majority of whom were discontinued from Actemra IV 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 IV 8 mg/kg plus DMARD. A total of 5,8 % of patients experienced an elevation of indirect bilirubin of > 1 to 2x ULN and 0,4 % had an elevation of > 2x 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 VI, MTX-naïve adult patients with moderate to severe, active early RA (mean disease duration ≤ 6-months) experienced more transient elevations in ALT above 3 x ULN compared with the all control population. This was observed in both Actemra-treated patients and MTX-monotherapy patients.

Elevations in lipid parameters

IV administration

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 have been reported commonly (see WARNINGS AND SPECIAL PRECAUTIONS).

Approximately 24 % of patients receiving Actemra IV 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.

Post-Marketing

The following adverse drug reactions have been identified from post marketing experience with Actemra (Table 4) based on spontaneous case reports, literature cases and cases from non-interventional study programs. Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 4: Adverse drug reactions from post marketing experience

Adverse reaction (MedDRA)	Incidence[4]	Frequency Category
Immune System Disorders		
Anaphylaxis (fatal)[1, 2]	Not observed in clinical trials	Rare
Skin and Subcutaneous Tissue Disorders		
Stevens-Johnson syndrome[3]	Not observed in clinical trials	Rare
Blood and lymphatic system disorders		
Hypofibrinogenaemia	1,3 per 100 patient years	Common
Hepatobiliary disorders		
Medicine-induced liver injury	0,2 per 100 patient years	Rare
Hepatitis	0,035 per 100 patient years	Rare
Hepatic failure	0,004 p er 100 patient years	Very Rare
Jaundice[3]	Not observed in clinical trials	Rare

[1] See *Contraindications*

[2] See *Warnings and Special Precautions*

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

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

4.9 Overdose

Clinical experience

There are limited data available on overdose with Actemra SC. One case of accidental overdose was reported in which a patient with multiple myeloma received a single dose of 40 mg/kg IV. No adverse reactions were observed.

No serious adverse reactions were observed in healthy volunteers who received a single dose up to 28 mg/kg, although dose limiting neutropenia was observed.

Treatment is palliative and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Tocilizumab binds 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

The pharmacokinetic properties (PK) of tocilizumab (TCZ) is characterised by non-linear elimination which is a combination of linear clearance and Michaelis-Menten elimination. The non-linear part of tocilizumab elimination leads to an increase in exposure that is more than dose-proportional. The pharmacokinetic parameters of tocilizumab do not change with time and are similar in healthy subjects and RA patients. Data from any patient population tested so far indicate no relationship between apparent clearance and the presence of anti-tocilizumab antibodies.

The summary of the PK of tocilizumab below applies to data collected in adult patients with Rheumatoid Arthritis (RA), adult patients with Giant Cell Arteritis (GCA) and paediatric patients with polyarticular Juvenile Idiopathic Arthritis (pJIA), all analysed using population PK monitoring.

Absorption

Following subcutaneous (SC) dosing in tocilizumab, peak serum concentrations are achieved by approximately 2,8 or 3,0 days (T_{max}) of dosing after weekly dosing in RA and GCA patient populations. After every other week dosing the median T_{max} was 4,5 or 4,7 days in RA and GCA patient populations. The relative bioavailability for the SC formulation was estimated to be 80 % in the RA and GCA populations.

Bioavailability was higher in paediatric patients with pJIA with the value estimated to be 96 %.

Bioavailability was higher in paediatric patients with pJIA with the value estimated to be 95 %.

Distribution

In RA and GCA populations, the central volume of distribution was 3,72 ℓ and 4,09 ℓ, while the peripheral volume of distribution was 3,37 ℓ and 3,37 ℓ resulting in a total volume of distribution at steady state of 7,07 ℓ and 7,46 ℓ, respectively.

Corresponding values in the paediatric pJIA population were central volume of distribution of 1,97 ℓ, and peripheral volume of distribution of 2,03 ℓ, respectively, resulting in a total volume of distribution at steady state of 4,0 ℓ.

Corresponding values in the paediatric sJIA population were central volume of distribution of 1,87 ℓ, [the] and peripheral volume of distribution of 2,14 ℓ, respectively, resulting in a total volume of distribution at steady state of 4,01 ℓ.

Elimination

The total clearance of tocilizumab is concentration-dependent and is the sum of the linear clearance and the non-linear clearance. 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. At

high concentrations, linear clearance was estimated to be 9,5 and 6,7 mℓ/h in RA and GCA populations, respectively.

In paediatric patients with pJIA, linear clearance was estimated to be 6,25 mℓ/h. Due to the impact of non-linear clearance, the t½ of tocilizumab varies with concentration. After subcutaneous administration following 162 mg every week at steady state, apparent t½ is up to 12,4 days and 18,9 days while after 162 mg every other week the apparent t½ is up to 5,3 days and 7,9 days, in RA and GCA populations, respectively.

In the pJIA population, a body weight regimen was employed with patients < 30 kg receiving 162 mg every 3 weeks, while patients with body weight ≥ 30 kg received 162 mg every 2 weeks in order to ensure similar exposure across the body weight range. Estimates of apparent t½ in patients with pJIA < 30 kg was up to 10,3 days and in patients with pJIA ≥ 30 kg were 7,1.

In children with sJIA, the effective $t_{1/2}$ of IV tocilizumab is up to 16 days for both the 12 mg/kg and 8 mg/kg Q2W regimens during a dosing interval at steady-state [99]. Following subcutaneous administration, the effective $t_{1/2}$ of tocilizumab in sJIA patients is up to 14 days for both the 162 mg QW and Q2W regimens during a dosing interval at steady state.

Time to Steady State

Based on the concentration dependent t½, time to steady-state varies by population and regimen. Following the 162 mg every week regimen approximately 90 % of steady state exposure for all PK parameters (C_{trough}, C_{max}, AUC_{τ}) was achieved by 12 and 17 weeks of dosing in RA and GCA populations. Following the 162 mg every other week regimen approximately 90 % of steady state exposure was achieved by 12 and 16 weeks of dosing in RA and GCA populations.
In paediatric patients with pJIA, regardless of body weight, steady-state was reached by 12 weeks of dosing.

The tables below provide a summary of the exposure parameters in adult and paediatric patients after SC dosing with tocilizumab. C_{mean}, the mean concentration over the dosing period is included to aid in characterising the comparative exposure better than AUC_T for dosing regimens with different inter-dose intervals. The bottom half of the table shows the accumulation i.e., ratio of exposure at steady state compared to exposure after a single dose of tocilizumab by regimen and population.

Table 1: Model-estimated mean ± SD PK parameters of tocilizumab at steady-state after SC dosing in adult patients with RA or GCA

	RA		**GCA**	
TCZ PK Parameter	**Q2W**	**QW**	**Q2W**	**QW**
C_{max} (µg/mℓ)	13,2 ± 8,8	49,8 ± 21,0	19,3 ± 12,8	73 ± 30,4
C_{trough} (µg/mℓ)	5,7 ± 6,8	43,0 ± 19,8	11,1 ± 10,3	68,1± 29,5
C_{mean} (µg/mℓ)	10,2 ± 8,0	47,4 ± 20,5	16,2 ± 11,8	71,3 ± 30,1
Accumulation C_{max}	2,12	5,27	2,26	8,88
Accumulation C_{trough}	6,02	6,30	5,61	9,59
Accumulation C_{mean} or AUC_T *	2,67	6,32	2,81	10,91

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

In GCA, tocilizumab concentrations at steady state are 50 % higher relative to average concentrations in the RA population. These differences occur due to unknown reasons. PK differences are not accompanied by marked differences in PD parameters and so the clinical relevance is not known.

Table 2. Model-estimated mean ± SD PK parameters of tocilizumab at steady-state after SC dosing in paediatric patients with pJIA

	pJIA	
TCZ PK Parameter	**162 mg Q3W** **below 30 kg**	**162 mg Q2W** **≥ 30 kg**
C_{max} (µg/mℓ)	75,5 ± 24,1	29,4 ± 13,5
C_{trough} (µg/mℓ)	18,4 ± 12,9	11,8 ± 7,08
C_{mean} (µg/mℓ)	45,5 ± 19,8	21,7 ± 10,4
Accumulation C_{max}	1,32	1,72
Accumulation C_{trough}	2,08	3,58
Accumulation C_{mean} or AUC_{τ} *	1,46	2,04

*τ = 2 week or 3 week for the two SC regimens, respectively

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

Approximately one-third of the patients in the GCA study had moderate renal impairment at baseline (estimated creatinine clearance of 30-59 mℓ/min). No impact on tocilizumab exposure was noted in these patients.

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

Hepatic impairment

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

Other Special Populations

Population pharmacokinetic analyses in adult RA and GCA patients showed that age, sex and ethnic origin did not affect the pharmacokinetics of tocilizumab.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients: l-arginine, l-arginine hydrochloride, l-histidine, l-histidine hydrochloride monohydrate, l-methionine, polysorbate 80 and water for injection

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store pre-filled syringe between 2 - 8 °C, in a refrigerator. Do not freeze.

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

Store all medicines out of reach of children.

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

Once removed from the refrigerator, Actemra SC must be administered within 8 hours and should not be kept at or above 30 °C.

Do not use if the medicine is cloudy or contains particles, is any colour besides colourless to slightly yellowish, or if any part of the pre-filled syringe appears to be damaged.

Any unused product or waste material should be disposed of.

6.5 Nature and contents of container

4 single-use pre-filled syringes.

The pre-filled syringe is composed of the following parts:

- A green plunger with a grey butyl rubber stopper.
- A type 1 glass barrel containing 0,9 ml of solution. The solution must be clear to strongly opalescent and colourless to slightly yellowish in colour.

A stainless steel needle enclosed with a protective shield (needle safety device) made of an elastomer seal covered with a rigid polypropylene shell.

6.6 Special precautions for disposal and other handling

After removing the pre-filled syringe from the refrigerator the pre-filled syringe should be allowed to reach room temperature (18 to 28 °C) by waiting for 25 - 30 minutes, before injecting Actemra SC.

The syringe should not be shaken. After removing the cap the injection should be started within 5 minutes, to prevent the medicine from drying out and blocking the needle. If the pre-filled syringe is not used within 5 minutes of removing the cap, it must be disposed of in a puncture-resistant container and a new pre-filled syringe used.

If, following insertion of the needle, the healthcare professional (HCP) cannot depress the plunger, the pre-filled syringe must be disposed of and a new pre-filled syringe used.

Actemra SC should not be used if it is cloudy or contains particles, is any colour besides colourless to slightly yellowish, or if any part of the pre-filled syringe appears to be damaged.

Disposal of syringes/sharps

The following points should be strictly adhered to regarding the use and disposal of the pre-filled syringe:

- Syringes should never be reused.
- Place all used syringes into a sharps container (puncture-proof disposable container).
- Keep the container out of the reach of children.
- Placing used sharps containers in the household waste should be avoided.
- Dispose of the full container according to local requirements or as instructed by your healthcare provider.

For home use, patients should procure a puncture-resistant container for the disposal of used syringe.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road

Hertford Office Park

Building E, Vorna Valley

Midrand, Johannesburg, 1686

South Africa

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

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