*WARNING: To be sold by retail on the prescription of Rheumatologist and Orthopedicians only*

# Tocilizumab Injection

Actemra®
अॅक्टेंमरा®

**WARNING: RISK OF SERIOUS INFECTIONS**

Patients treated with Actemra are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions, Undesirable Effects]*.

Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt Actemra until the infection is controlled.

Reported infections include:

- Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before Actemra use and during therapy. Treatment for latent infection should be initiated prior to Actemra use.
- Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.
- Bacterial, viral and other infections due to opportunistic pathogens.

The risks and benefits of treatment with Actemra should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Actemra, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *[see Warnings and Precautions]*.

## 1. DESCRIPTION

### 1.1 Therapeutic/Pharmacologic Class of Drug

Tocilizumab is a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass.

ATC Code: L04AC07.

### 1.2 Type of Dosage Form and Strength

Dosage form: Subcutaneous (SC) formulation. Ready-to-use sterile liquid solution in a single-use pre-filled syringe (PFS) with needle safety device (NSD).

Strength: 180 mg/ml

### 1.3 Route of Administration

Subcutaneous (SC) injection.

### 1.4 Sterile/Radioactive Statement

Sterile

### 1.5 Qualitative and Quantitative Composition

Active ingredient: tocilizumab

Excipients: Polysorbate 80, L-Arginine, L-Arginine Hydrochloride, L-Methionine, L-Histidine, L-Histidine Hydrochloride Monohydrate, Water for Injection.

Tocilizumab solution for subcutaneous (SC) injection is a yellowish, preservative free liquid supplied in a ready-to-use, single-use pre-filled syringe with needle safety device (PFS+NSD). Each device delivers 0.9 mL (162 mg) of tocilizumab.

## 2. CLINICAL PARTICULARS

### 2.1 Therapeutic Indications

**Rheumatoid Arthritis (RA)**

Tocilizumab SC (subcutaneous) formulation, in combination with methotrexate (MTX), is indicated for

- the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX.
- the treatment of moderate to severe active 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, Tocilizumab can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

**Giant Cell Arteritis (GCA) [SC formulation only]**

Tocilizumab is indicated in combination with tapering glucocorticoid therapy for the treatment of giant cell arteritis (GCA) only in adult patients requiring no more than 60mg prednisone per day (or an equivalent drug) at initiation of Tocilizumab with regimen as follows:-

Dosage in patients with new-onset GCA: 162mg s.c. every two weeks, combined with a tapering course of glucocorticoids.

Dosage in patients with relapsing GCA: 162mg s.c. once weekly, combined with a tapering course of glucocorticoids.

**2.2 Dosage and Administration**

*General*

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

For adult patients with RA, tocilizumab is administered as an SC injection.

For adult patients with GCA, tocilizumab is administered as a SC injection.

Subcutaneous Administration

Tocilizumab SC formulation is not intended for intravenous administration.

Tocilizumab SC formulation is administered with a single-use PFS+NSD. The first injection should be performed under the supervision of a qualified health care professional. A patient can self-inject Actemra only if the physician determines that it is appropriate and the patient agrees to medical follow-up as necessary and has been trained in proper injection technique. The recommended injection sites (abdomen, thigh and upper arm) should be rotated and injections should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

Patients who transition from tocilizumab 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 health care professional.

Assess suitability of patient or parent/guardian for SC home administration and instruct the patient or parent/guardian to inform a healthcare professional before administering the next dose, if any symptoms of allergic reaction are experienced.

Patients should seek immediate medical attention if they develop symptoms of serious allergic reactions (see section 2.4.1 Warnings and Precautions, General and 2.6 Undesirable Effects).

**Rheumatoid Arthritis**

Tocilizumab may be used as monotherapy or concomitantly with methotrexate or other non-biologic DMARDs as a subcutaneous injection.

The recommended dosage regimen of Subcutaneous tocilizumab for adult RA patients:

| | |
|---|---|
| Patients less than 100 kg weight | 162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response |
| Patients at or above 100 kg weight | 162 mg administered subcutaneously every week |

When transitioning from Tocilizumab intravenous therapy to subcutaneous administration, administer the first subcutaneous dose instead of the next scheduled intravenous dose.

Interruption of dose or reduction in frequency of administration of subcutaneous dose from every week to every other week dosing is recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia.

**Giant Cell Arteritis (GCA) [SC formulation only]**

Dosage in patients with new-onset GCA: 162mg s.c. every two weeks, combined with a tapering course of glucocorticoids.

Dosage in patients with relapsing GCA: 162mg s.c. once weekly, combined with a tapering course of glucocorticoids.

*Dose Modification Recommendations for RA and GCA:*
(*see section 2.4.1Warnings and Precautions, General* )

- Liver enzyme abnormalities

| **Laboratory Value** | **Action** |
|---|---|

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

- Low absolute neutrophil count (ANC)

| **Laboratory Value (cells x $10^9$/L)** | **Action** |
|---|---|
| ANC > 1 | Maintain dose |
| ANC 0.5 to 1 | Interrupt tocilizumab dosing<br><br>For patients on subcutaneous tocilizumab, when ANC > 1 x $10^9$/L resume tocilizumab injection every other week and increase frequency to every week, as clinically appropriate. |
| ANC < 0.5 | Discontinue tocilizumab |

- Low platelet count

| **Laboratory Value (cells x $10^3$/μL)** | **Action** |
|---|---|
| 50 to 100 | Interrupt tocilizumab dosing<br><br>For patients on subcutaneous tocilizumab, when platelet count is > 100 x $10^3$/μL resume tocilizumab injection every other week and increase frequency to every week, as clinically appropriate. |

| | |
|---|---|
| < 50 | Discontinue tocilizumab |

### 2.2.1 Special Dosage Instructions

*Pediatric use:* No text

*Geriatric use:* No dose adjustment is required in elderly patients > 65 years of age.

*Renal impairment*: No dose adjustment is required in patients with mild or moderate renal impairment (see section 3.2.5 *Pharmacokinetics in Special Populations*). Tocilizumab has not been studied in patients with severe renal impairment..

*Hepatic impairment:* The safety and efficacy of tocilizumab has not been studied in patients with hepatic impairment (see section 2.4.1 Warnings and Precautions, General).

## 2.3 Contraindications

Actemra is contraindicated in patients with a known hypersensitivity to tocilizumab or to any of the excipients.

## 2.4 Warnings and Precautions

### 2.4.1 General

In order to improve the traceability of biological medicinal products, the trade name and batch number of the administered product should be clearly recorded (or stated) in the patient file.

*Infections*

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including tocilizumab (see section 2.6, Undesirable Effects). Tocilizumab treatment should not be initiated in patients with active infections. Administration of tocilizumab should be interrupted if a patient develops a serious infection until the infection is controlled. Healthcare professionals should exercise caution when considering the use of tocilizumab in patients with a history of recurring infection 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 immunosuppressive agents, such as tocilizumab, as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute phase reactants. 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 healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

*Complications of diverticulitis*

Events of diverticular perforation as complications of diverticulitis have been reported in patients treated with tocilizumab. Tocilizumab 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, should be evaluated promptly for early identification of gastrointestinal perforation.

*Tuberculosis*

As recommended for other biologic therapies in all patients should be screened for latent tuberculosis infection prior to starting tocilizumab therapy. Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before initiating tocilizumab.

*Vaccinations*

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

In a randomized open-label study, adult RA patients treated with tocilizumab 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 pediatric or elderly patients, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating tocilizumab therapy. The interval between live vaccinations and initiation of tocilizumab therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

*Hypersensitivity Reactions*

Serious hypersensitivity reactions, including anaphylaxis have been reported in association with tocilizumab (*see section 2.6.1 Undesirable Effects, Clinical Trials*). In the post marketing setting, events of serious hypersensitivity and anaphylaxis have occurred in patients treated with a range of doses of tocilizumab, with or without concomitant therapies, premedication, and / or a previous hypersensitivity reaction. In the post marketing setting, cases with a fatal outcome have been reported with intravenous

tocilizumab. These events have occurred as early as the first infusion of tocilizumab (*see sections 2.3 Contraindications, 2.6.2 Post Marketing*). Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during infusion with tocilizumab. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of tocilizumab should be stopped immediately and tocilizumab should be permanently discontinued (*see section 2.2 Dosage and Administration*).

*Active Hepatic Disease and Hepatic Impairment*

Treatment with tocilizumab particularly when administered concomitantly with methotrexate, may be associated with elevations in hepatic transaminases therefore caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment (see section *2.2.1 Special Dosage Instructions*, 2.6.1 *Undesirable Effects, Clinical Trials*).

*Hepatotoxicity*

Mild and moderate elevations of hepatic transaminases have been observed with tocilizumab treatment (*see section 2.6.1 Undesirable Effects, Clinical Trials*). Increased frequency of these elevations was observed when drugs, which are known to cause hepatotoxicity (e.g. methotrexate (MTX)), were used in combination with tocilizumab.

Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, have been observed with tocilizumab (*see section 2.6.2 Undesirable Effects, Post Marketing Experience*). Serious hepatic injury occurred between 2 weeks to more than 5 years after initiation of tocilizumab. Cases of liver failure resulting in liver transplantation have been reported.

Caution should be exercised when considering initiation of tocilizumab treatment in patients with elevated transaminases ALT or AST above 1.5x ULN. In patients with elevated ALT or AST above 5x ULN treatment is not recommended.

In RA, GCA, pJIA, sJIA, ALT/AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended dose modifications, including tocilizumab discontinuation, based on transaminases levels, see section 2.2 Dosage and Administration.

*Viral reactivation*

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

*Demyelinating disorders*

Physicians should be vigilant for symptoms potentially indicative of new onset central demyelinating disorders. The potential for central demyelination with tocilizumab is currently unknown.

*Neutropenia*

Treatment with tocilizumab was associated with a higher incidence of neutropenia. Treatment-related neutropenia was not associated with serious infection in clinical trials (*see section 2.6.1 Undesirable Effects, Clinical Trials*).

Caution should be exercised when considering initiation of tocilizumab treatment in patients with a low neutrophil count i.e. absolute neutrophil count (ANC) below 2 x $10^9$/L. In patients with an absolute neutrophil count below 0.5 x $10^9$/L treatment is not recommended.

In RA and GCA, the neutrophil count 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 results, see section 2.2 Dosage and Administration.

In pJIA and sJIA, the neutrophil count should be monitored at the time of the second administration and thereafter according to good clinical practice (*see section 2.2 Dosage and Administration, Dose modifications*).

*Thrombocytopenia*

Treatment with tocilizumab 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 2.6.1 Undesirable Effects, Clinical Trials*).

Caution should be exercised when considering initiation of tocilizumab 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 platelet counts, see section 2.2 Dosage and Administration.

In pJIA and sJIA, platelets should be monitored at the time of the second administration and thereafter according to good clinical practice (see section 2.2 Dosage and Administration, Dose modifications).

*Lipids parameters*

Elevations of lipid parameters such as total cholesterol, triglycerides and/or low density lipoprotein (LDL) cholesterol have been observed (*see section 2.6.1Undesirable Effects, Clinical Trials*).

In patients treated with tocilizumab, assessment of lipid parameters should be performed 4 to 8 weeks following initiation of tocilizumab therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

***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.

### 2.4.2 Drug Abuse and Dependence

No studies on the effects on the potential for tocilizumab to cause dependence have been performed. However, there is no evidence from the available data that tocilizumab treatment results in dependence.

### 2.4.3 Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machine have been performed. However, there is no evidence from the available data that tocilizumab treatment affects the ability to drive and use machines.

## 2.5 Use in Special Populations

### 2.5.1 Pregnancy

There are no adequate data from the use of tocilizumab in pregnant women. A study in monkeys did not indicate any dysmorphogenic potential but has yielded a higher number of spontaneous abortion/embryo-foetal death at a high dose (see section 3.3.5 Non-clinical Safety, Other). The relevance of these data for humans is unknown.

Tocilizumab should not be used during pregnancy unless clearly indicated by medical need.

### 2.5.2 Labour and Delivery

No text

### 2.5.3 Nursing Mothers

It is unknown whether tocilizumab is excreted in human breast milk. Although endogenous immunoglobulins of the IgG isotope are secreted into human milk, a systemic absorption of tocilizumab via breast feeding is unlikely due to the rapid proteolytic degradation of such proteins in the digestive system. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with tocilizumab should be made taking into account the benefit of breast-feeding to the child and the benefit of tocilizumab therapy to the woman.

### 2.5.4 Paediatric Use
(See section 2.2.1 Special Dosage Instructions).

### 2.5.5 Geriatric Use
(See section 2.2.1 Special Dosage Instructions, section 3.2.5 Pharmacokinetics in Special Populations).

### 2.5.6 Renal Impairment
(See section 2.2.1 Special Dosage Instructions, section 3.2.5 Pharmacokinetics in Special Populations).

### 2.5.7 Hepatic Impairment
(See section 2.2.1 Special Dosage Instructions, section 3.2.5 Pharmacokinetics in Special Populations).

## 2.6 Undesirable Effects

### 2.6.1 Clinical Trials

The safety profile in this section comes from 4510 patients exposed to tocilizumab in clinical trials; the majority of these patients were participating in RA studies (n=4009) while the remaining experience comes from pJIA (n=240), sJIA (n=112), and GCA (n=149) studies. The safety profile of tocilizumab across these indications remains similar and undifferentiated.

Adverse Drug Reactions (ADRs) from clinical trials (Table 1) is listed by MedDRA system organ class according to clinical importance to the patient. The corresponding frequency category for each ADR is based on the following convention: very common (≥1/10), common (≥1/100 to < 1/10) or uncommon (≥1/1000 to < 1/100).

***Table 1: Summary of ADRs occurring in patients treated with Tocilizumab***

| System Organ Class | Very Common | Common | Uncommon |
|---|---|---|---|
| Infections and infestations | Upper respiratory tract infections | Cellulitis, 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 | | Hepatic transaminases increased, Weight increased, | Total bilirubin increased |

| | | | |
|---|---|---|---|
| Vascular disorders | | Hypertension | |
| Blood and lymphatic system disorders | | Leukopenia, Neutropenia | |
| Metabolism and nutrition disorders | | Hypercholesterolaemia | Hypertriglyceridaemia |
| General disorders and administration site conditions | Injection site reaction | Peripheral oedema Hypersensitivity reactions, Injection site reaction | |
| Respiratory, thoracic and mediastinal disorders | | Cough, Dyspnoea | |
| Eye disorders | | Conjunctivitis | |
| Renal disorders | | | Nephrolithiasis |
| Endocrine disorders | | | Hypothyroidism |

***Description of selected adverse drug reactions from clinical trials:***

**Rheumatoid Arthritis**

***Patients Treated with Intravenous Tocilizumab:***

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

The *all control* population includes all patients from the double-blind phases of each core study from randomization until either the first change in the treatment regimen, or two years is reached. The control period in 4 of the studies was 6 months and in 1 study was up to 2 years. In the double-blind controlled studies, 774 patients received tocilizumab 4 mg/kg in combination with MTX, 1870 patients received Tocilizumab 8 mg/kg in combination with MTX/other DMARDs, and 288 patients received tocilizumab 8 mg/kg monotherapy.

The *all exposure* population includes all patients who received at least one dose of tocilizumab either in the double-blind control period or open label extension phase in studies. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3296 for at least one year; 2806 received treatment for at least 2 years and 1222 for 3 years.

***Infections***

In the 6-month controlled trials, the rate of all infections reported with tocilizumab 8 mg/kg + DMARD treatment was 127 events per 100 patient (pt) years compared to 112

events per 100 pt years in the placebo + DMARD group. In the *all exposure* population, the overall rate of infections with tocilizumab was 108 events per 100 pt years exposure.

In 6-month controlled clinical trials, the rate of serious infections (bacterial, viral and fungal) with tocilizumab 8 mg/kg + DMARD was 5.3 events per 100 pt years exposure compared to 3.9 events per 100 pt years exposure in the placebo+ DMARD group. In the monotherapy study the rate of serious infections was 3.6 events per 100 pt years of exposure in the tocilizumab group and 1.5 events per 100 pt years of exposure in the MTX group.

In the *all exposure* population, the overall rate of serious infections was 4.7 events per 100 pt years. Reported serious infections, some with fatal outcome, included pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis, bacterial arthritis. Cases of opportunistic infections have also been reported.

***Gastrointestinal Perforation***
During the 6 month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 pt years with tocilizumab therapy. In the *all exposure* population the overall rate of gastrointestinal perforation was 0.28 events per 100 pt years. Reports of gastrointestinal perforation on tocilizumab were primarily reported as complications of diverticulitis including generalized purulent peritonitis, lower GI perforation, fistula and abscess.

***Infusion reactions***
In the 6-month controlled trials adverse events associated with infusion (selected events occurring during or within 24 hours of infusion) were reported by 6.9% of patients in the tocilizumab 8 mg/kg + DMARD and 5.1% of patients in the placebo + 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 anaphylaxis (occurring in a total of 6/3778 patients) was several-fold higher in the 4 mg/kg arm in comparison to the 8 mg/kg dose. Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation, were reported in a total of 13 out of 3778 patients (0.3%) treated with tocilizumab during the controlled and open label clinical trials. These reactions were generally observed during the second to fifth infusions of tocilizumab (*see section 2.4.1 Warnings and Precautions, General*).

***Immunogenicity***
A total of 2876 patients have been tested for anti-tocilizumab antibodies in the 6-month controlled clinical trials. Forty six patients (1.6%) developed positive anti-tocilizumab antibodies of whom 5 had an associated medically significant hypersensitivity reaction leading to withdrawal. Thirty patients (1.1%) developed neutralising antibodies.

***Early Rheumatoid Arthritis***

Study VI (WA19926) evaluated 1162 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 tocilizumab treatment groups was consistent with the known safety profile of tocilizumab (see Table 1) (*see section 3.1.2 Clinical/Efficacy Studies*).

***Monotherapy: tocilizumab versus adalimumab***

In a 24 week double-blinded, parallel study (monotherapy with tocilizumab 8 mg/kg IV q4w (N=162) compared to adalimumab 40 mg SC q2w (N=162)), the overall clinical adverse event profile was similar between tocilizumab and adalimumab. The proportion of patients with serious adverse events was balanced between the treatment groups (tocilizumab 11.7% vs. adalimumab 9.9%) with the most common event being infections (3.1% each). Both study treatments induced the same pattern of changes in laboratory safety parameters (decreases in neutrophil and platelet counts, increases in ALT, AST and lipids), however, the magnitude of change and the frequency of marked abnormalities was higher with tocilizumab compared with adalimumab. Four (2.5%) patients in the tocilizumab arm and two (1.2%) patients in the adalimumab arm experienced CTC grade 3 or 4 neutrophil count decreases. Eleven (6.8%) patients in the tocilizumab arm and five (3.1%) patients in the adalimumab arm experienced ALT increases of CTC grade 2 or higher. The mean LDL increase from baseline was 0.64 mmol/L (25 mg/dL) for patients in the tocilizumab arm and 0.19 mmol/l (7 mg/dL) for patients in the adalimumab arm. The safety observed in the tocilizumab arm was consistent with the known safety profile of tocilizumab and no new or unexpected adverse drug reactions were observed (see Table 1) (*see section 3.1.2 Clinical/Efficacy Studies*).

***Patients Treated with Subcutaneous Tocilizumab***

The safety of subcutaneous tocilizumab in RA was studied in SC-I. The study compared the efficacy and safety of tocilizumab 162 mg administered every week SC versus 8 mg/kg IV in 1262 subjects with adult RA. All patients in the study received background non-biologic DMARD(s). The safety and immunogenicity observed for tocilizumab administered SC was consistent with the known safety profile of IV tocilizumab and no new or unexpected adverse drug reactions were observed (see Table 1). A higher frequency of injection site reactions (ISRs) was observed in the SC arms compared with placebo SC injections in the IV arms (see section 3.1.2 Clinical/Efficacy Studies).

***Injection Site Reactions (ISRs)***

During the 6-month controlled period, in SC-I, the frequency of ISRs was 10.1% (64/631) and 2.4% (15/631) for the SC tocilizumab and the SC placebo (IV group) weekly injections, respectively. These ISRs (including erythema, pruritus, pain and haematoma) were mild to moderate in severity. The majority was resolved without any treatment and none necessitated drug discontinuation.

***Immunogenicity***

In SC-I, a total of 625 patients treated with tocilizumab 162 mg weekly were tested for anti-tocilizumab antibodies in the 6 month controlled period. Five patients (0.8%)

developed positive anti-tocilizumab antibodies; of these, all developed neutralizing anti-tocilizumab antibodies.
A total of 1454 SC tocilizumab 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 neutralizing anti-tocilizumab antibodies.

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

**Giant Cell Arteritis**

The safety of subcutaneous tocilizumab has been studied in one Phase III study (WA28119) with 251 GCA patients. The total patient years duration in the tocilizumab 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 tocilizumab treatment groups was consistent with the known safety profile of tocilizumab (see Table 1) (*see section 3.1.2 Clinical/Efficacy Studies*).

***Infections***

The rate of infection/serious infection events was balanced between the tocilizumab 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 tocilizumab was studied in 240 pediatric patients with pJIA. In Study WA19977, 188 patients, (2 to 17 years of age),were treated with IV tocilizumab and in Study WA28117, 52 patients (1 to 17 years of age) were treated with SC tocilizumab. The total patient exposure in the tocilizumab in the pJIA all exposure population was 184.4 patient years for IV tocilizumab and 50.4 patient years for SC tocilizumab. In general, the safety profile observed in patients with pJIA was consistent with the known safety profile of tocilizumab with the exception of ISRs (see Table 1). A higher frequency of ISRs was experienced by pJIA patients following SC tocilizumab injections compared to adult RA patients (*see Undesirable Effects section*).

***Infections***

Infections are the most common observed events in pJIA. The rate of infections in the PJIA IV tocilizumab 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 Tocilizumab (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 tocilizumab (21.4%) compared to patients weighing ≥30 kg, treated with 8 mg/kg tocilizumab (7.6%). The rate of infection in pJIA patients

treated with SC tocilizumab was comparable with pJIA patients treated with IV tocilizumab.

***Infusion Reactions***
In pJIA patients, infusion related reactions are defined as all events occurring during or within 24 hours of an infusion with IV tocilizumab. In the tocilizumab 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 (*see Undesirable Effects section*).

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

***Injection Site Reactions***
A total of 28.8% (15/52) pJIA patients experienced ISRs to SC tocilizumab. 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, hematoma, 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.

***Immunogenicity***
Across the two studies in pJIA patients, a total of four patients (0.5% [1/188] in the IV Study WA19977 and 5.8% [3/52] in the SC Study WA28117) developed positive neutralizing anti-tocilizumab antibodies without developing a serious or clinically significant hypersensitivity reaction. Of these 4 patients, 2 subsequently withdrew from the study. No correlation between antibody development and clinical response or adverse events was observed.

**Systemic Juvenile Idiopathic Arthritis -**

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

***Infections***
In the 12 week controlled trial (Study WA 18221), the rate of all infections in the IV tocilizumab group was 344.7 per 100 patient-years and 287.0 per 100 patient-years in the placebo group. In the 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 (Study WA18221), the rate of serious infections in the IV tocilizumab group was 11.5 per 100 patient years. In the open label extension study the overall rate of serious infections 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.

The rate of infection in sJIA patients treated with SC tocilizumab was comparable to sJIA patients treated with IV tocilizumab.

***Infusion Reactions***
For sJIA patients, infusion related reactions are defined as all events occurring during or within 24 hours of an infusion with IV tocilizumab. In the 12 week controlled trial (Study WA18221), four percent (4.0%) of patients from the tocilizumab 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 experience, 16% of patients in the IV tocilizumab group and 5.4% of patients in the placebo group experienced an event within 24 hours of infusion. In the tocilizumab group, the events included, but 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 IV tocilizumab and requiring treatment discontinuation, were reported in 1 out of 112 patients (below 1%) treated with tocilizumab during the controlled and open-label parts of the clinical trial.

***Injection Site Reactions (ISRs)***
In Study WA28118, a total of 41.2% (21/51) sJIA patients experienced ISRs to SC tocilizumab. 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

***Immunogenicity***
In Study WA 18221, 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. 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

**Laboratory Abnormalities**

**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**

*Intravenous Administration:*
In the 6-month controlled trials decreases in neutrophil counts below 1 x $10^9$/ L occurred in 3.4% of patients on tocilizumab 8 mg/kg + DMARD compared to below 0.1% of patients on placebo + DMARD. Approximately half of the instances of ANC below 1 x $10^9$/ L occurred within 8 weeks after starting therapy. Decreases below 0.5 x $10^9$/ L were reported in 0.3% patients receiving tocilizumab 8 mg/kg + DMARD (*see sections 2.2 Dosage and Administration, 2.4.1 Warnings and Precautions*).

In the *all control* and *all exposure* population, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 6-month controlled clinical trials.

*Subcutaneous Administration:*
During routine laboratory monitoring in the tocilizumab 6-month controlled period of clinical trial SC-I, a decrease in neutrophil count below 1 × $10^9$/L occurred in 2.9% of patients on tocilizumab 162 mg SC weekly.

**Giant Cell Arteritis**

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 tocilizumab SC weekly group. This was not observed in either of the placebo plus prednisone taper groups.

**Polyarticular Juvenile Idiopathic Arthritis**

During routine laboratory monitoring in the tocilizumab all exposure population, a decrease in neutrophil count below 1 × $10^9$/L occurred in 3.7% of patients treated with IV tocilizumab and 15.4% of patients treated with SC tocilizumab.

**Systemic Juvenile Idiopathic Arthritis**

During routine laboratory monitoring in the 12 week controlled trial (Study WA18221), a decrease in neutrophil counts below 1 × $10^9$/L occurred in 7% of patients in the IV tocilizumab group, and in none in the placebo group.

In the open-label extension study (WA18221) decreases in neutrophil counts below 1 x $10^9$/L, occurred in 15% of the tocilizumab group.

In the 52-week open-label trial (Study WA28118), neutrophil count decrease below 1 × $10^9$/L occurred in 23.5% of patients treated with SC tocilizumab.

***Platelets***

**Rheumatoid Arthritis**

*Intravenous Administration:*
In the 6-month controlled trials decreases in platelet counts below 100 x $10^3$/ µl occurred in 1.7% of patients on tocilizumab 8 mg/kg plus traditional DMARDs compared to below 1% on placebo plus traditional DMARDs. These decreases occurred without associated bleeding events (*see sections 2.2 Dosage and Administration, 2.4.1 Warnings and Precautions* )

In the *all control* and *all exposure* population, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 6-month controlled clinical trials.

*Subcutaneous Administration:*
During routine laboratory monitoring in the tocilizumab 6-month controlled period of clinical trial SC-I, none of the patients had a decrease in platelet count to $\leq 50 \times 10^3$ / µL.

**Giant Cell Arteritis**
During routine laboratory monitoring in the tocilizumab 12-month double blind, placebo-controlled phase of study WA28119, one patient (1%, 1/100) in the tocilizumab 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 tocilizumab all exposure population, a decrease in platelet count to $\leq 50 \times 10^3$ / µL occurred in 1% of patients treated with IV tocilizumab without associated bleeding events and in no patients treated with SC tocilizumab.

**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 $\leq 100 \times 10^3$ / 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 IV tocilizumab group, without associated bleeding events.

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

***Liver Enzyme elevations***

**Rheumatoid Arthritis**

*Intravenous Administration:*
During the 6-month controlled trials transient elevations in ALT/AST above 3 x ULN were observed in 2.1% of patients on tocilizumab 8 mg/kg compared to 4.9% of patients on MTX, and in 6.5% of patients who received tocilizumab 8 mg/kg + DMARD compared to 1.5% of patients on placebo + DMARDs. The addition of potentially hepatotoxic drugs (e.g. MTX) to tocilizumab monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST above 5 x ULN were observed in 0.7% of tocilizumab monotherapy patients and 1.4% of tocilizumab + DMARD patients, the majority of whom were discontinued from tocilizumab treatment (*see section 2.2 Dosage and Administration, 2.4.1 Warnings and Precautions*). During routine laboratory monitoring, the incidence of indirect bilirubin greater than the upper limit of normal was 6.2% in patients treated with 8 mg/kg Tocilizumab + DMARD in the *all control* population.

In the *all control* and *all 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 3xULN compared with the *all control* population. This was observed in both tocilizumab treated patients and MTX monotherapy patients.

In Study WA25204, of the 1538 patients with moderate to severe RA (*see Section 3.1.2 Clinical/Efficacy Studies*) and treated with tocilizumab, elevations in ALT or AST >3 x ULN occurred in 5.3% and 2.2% patients, respectively. One serious event of drug induced hepatitis with hyperbilirubinemia was reported in association with tocilizumab treatment (*see section 2.4.1 Warnings and Precautions*)

*Subcutaneous Administration:*
During routine laboratory monitoring in the tocilizumab 6-month controlled period of clinical trial SC-I, 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 tocilizumab 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 IV tocilizumab, and in 9.6% and 3.8% patients treated with SC Tocilizumab 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 Tocilizumab group, and in 0% of placebo patients.

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

***Elevations in Lipid parameters***

**Rheumatoid Arthritis**

*Intravenous Administration:*
During routine laboratory monitoring in the 6 month controlled trials, elevations in lipid parameters (total cholesterol, LDL, HDL, triglycerides) were observed in patients treated with tocilizumab. Approximately 24% of patients receiving tocilizumab in clinical trials experienced sustained elevations in total cholesterol above 6.2 mmol/ L (240 mg/dL), with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/ L (160 mg/dL).

In the majority of patients there was no increase in atherogenic indices, and elevations in total cholesterol responded to treatment with lipid-lowering agents.

In the *all control* and *all exposure* population, the pattern and incidence of elevations in lipid parameters remained consistent with what was seen in the 6 month controlled clinical trials.

*Subcutaneous Administration:*
During routine laboratory monitoring in the tocilizumab 6-month controlled period of clinical trial SC-I, 19% of patients on 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 SC weekly.

**Giant Cell Arteritis**

During routine laboratory monitoring in the tocilizumab 12-month double blind, placebo-controlled phase of study WA28119 [86], 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 tocilizumab SC weekly group.

**Polyarticular Juvenile Idiopathic Arthritis**

During routine laboratory monitoring in the IV tocilizumab 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 SC tocilizumab 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.

### 2.6.2 Post Marketing Experience

The following adverse drug reactions have been identified from post marketing experience with tocilizumab (Table 1a) 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 1a: 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** | | |
| Hypofibrinogenemia | 1.3 per 100 patient years | Common |
| **Hepatobiliary disorders** | | |
| Drug-induced liver injury | 0.027 per 100 patient years | Rare |
| Hepatitis | 0.035 per 100 patient years | Rare |
| Hepatic failure | 0.004 per 100 patient years | Very Rare |
| Jaundice[3] | Not observed in clinical trials | Rare |

[1] See section *2.3 Contraindications*
[2] See section *2.4.1 Warnings and Precautions, General*
[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 TCZ in clinical trials.
[4] Incidence rate calculated based on all-exposure data obtained from relevant completed clinical trials for all indications.

## 2.7 Overdose

There are limited data available on overdosage with tocilizumab. 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 drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received a single dose up to 28 mg/kg IV, although dose-limiting neutropenia was observed.

## 2.8 Interactions with other Medicinal Products and other Forms of Interaction

Population pharmacokinetic analyses did not detect any effect of MTX, nonsteroidal anti-inflammatory drugs or corticosteroids on tocilizumab clearance in RA patients. In GCA patients, no effect of cumulative corticosteroid dose on tocilizumab exposure was observed.

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.

Tocilizumab has not been studied in combination with other biological DMARDs.

The expression of hepatic CYP450 enzymes is suppressed by cytokines, such as IL-6, that stimulate chronic inflammation. Thus, CYP450 expression 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 normalizes 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 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 of these products may need to be adjusted to maintain their therapeutic effect. Given its long elimination half-life (t1/2), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

## 3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

### 3.1 Pharmacodynamic Properties

In clinical studies with tocilizumab in RA, rapid decreases in C-Reactive Protein (CRP), erythrocyte sedimentation rate (ESR), serum amyloid A and fibrinogen were observed. Increases in haemoglobin levels were observed, through tocilizumab decreasing the IL-6 driven effects on hepcidin production to increase iron availability.

In study WA28119, similar rapid decreases in CRP and ESR were observed along with slight increases in mean corpuscular haemoglobin concentration.

In healthy subjects administered tocilizumab in doses from 2 to 28 mg/kg, absolute neutrophil counts decreased to their lowest 3 to 5 days following administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. Rheumatoid arthritis patients and GCA patients demonstrated a similar pattern of absolute neutrophil counts following tocilizumab administration (*see section 2.4.1 Warning and Precautions, General*).

#### 3.1.1 Mechanism of action

Tocilizumab is a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin (Ig) $IgG_1$ subclass. Tocilizumab binds to both soluble and membrane-bound IL 6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit sIL-6R and mIL-6R-mediated signaling. IL-6 is a multifunctional cytokine, produced by a variety of cell types involved in local paracrine function as well as regulation of systemic physiological and pathological processes such as induction of immunoglobulin secretion, T-cell activation, induction of hepatic acute phase proteins and stimulation of haematopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis, and neoplasia.

The possibility exists for tocilizumab to affect host defences against infections and malignancies. The role of Il-6 receptor inhibition in the development of malignancies is not known.

### 3.1.2 Clinical / Efficacy Studies

**Rheumatoid Arthritis**
The efficacy of subcutaneously administered tocilizumab was assessed in a double-blind, controlled, multicentre study in patients with active RA. The study (SC-I) required patients to be above 18 years of age with active rheumatoid arthritis diagnosed according to ACR criteria and who had at least 4 tender and 4 swollen joints at baseline. All patients received background non-biologic DMARD(s).

Study SC-I evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to their existing rheumatologic therapy, including one or more DMARD(s). Approximately 20% had a history of inadequate response to at least one TNF inhibitor. In SC-I, 1262 patients were randomized 1:1 to receive tocilizumab SC 162 mg every week or tocilizumab IV 8 mg/kg every four weeks in combination with non-biologic DMARD(s). The primary endpoint in the study was the difference in the proportion of patients who achieved an ACR20 response at week 24. The results from study SC-I is shown in Table 2.

**Table 2: Clinical Response at Week 24 in Subcutaneous Trial (Percent of Patients)**

| | SC-I[a] | |
|---|---|---|
| | TCZ SC 162 mg week + DMARD(s) N=558 | TCZ IV 8 mg/kg + DMARD(s) N=537 |
| ACR20 | | |
| Week 24 | 69.4% | 73.4% |
| Weighted difference (95% CI) | -4.0 (-9.2, 1.2) | |
| ACR50 | | |
| Week 24 | 47.0% | 48.6% |
| Weighted difference (95% CI) | -1.8 (-7.5, 4.0) | |
| ACR70 | | |
| Week 24 | 24.0% | 27.9% |
| Weighted difference (95% CI) | -3.8 (-9.0, 1.3) | |
| Change in DAS28 [adjusted mean] | | |
| Week 24 | -3.5 | -3.5 |
| Weighted difference (95% CI) | 0 (-0.2, 0.1) | |
| DAS28 < 2.6 | | |
| Week 24 | 38.4% | 36.9% |
| Weighted difference (95% CI) | 0.9 (-5.0, 6.8) | |
| EULAR response (%) | | |
| None | 3.3% | 4.8% |
| Moderate | 41.7% | 42.7% |
| Good | 55.0% | 52.4% |

TCZ = tocilizumab
a = Per Protocol Population

*Radiographic Response – Subcutaneous Administration*
The radiographic response of subcutaneously administered tocilizumab was assessed in a double-blind, controlled, multicentre study in patients with active RA. This study (SC-II) evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to their existing rheumatologic therapy, including one or more DMARD(s) where approximately 20% had a history of inadequate response to at least one TNF inhibitor. Patients were required to be above 18 years of age with active rheumatoid arthritis diagnosed according to ACR criteria and who had at least 8 tender and 6 swollen joints at baseline. In SC-II, 656 patients were randomized 2:1 to tocilizumab SC 162 mg every other week or placebo, in combination with non-biologic DMARD(s).

In study SC-II, inhibition of structural joint damage was assessed radiographically and expressed as a change from baseline in the van der Heijde modified mean total Sharp

score (mTSS). At week 24, inhibition of structural damage was shown, with significantly less radiographic progression in patients receiving tocilizumab SC compared with placebo (mTSS of 0.62 vs. 1.23, p=0.0149 (van Elteren). These results are consistent with those observed in patients treated with intravenous tocilizumab.

*Quality of Life Outcomes – Subcutaneous Administration*

In study SC-I, the mean decrease in HAQ-DI from baseline to week 24 was 0.6 for both tocilizumab SC 162 mg weekly and tocilizumab IV 8 mg/kg every 4 weeks. The proportion of patients achieving a clinically relevant improvement in HAQ-DI at week 24 (change from baseline of ≥ 0.3 units) was comparable in the tocilizumab SC every week group (65.2%) versus the tocilizumab IV 8 mg/kg group (67.4%), with a weighted difference in proportions of -2.3% (95% CI -8.1, 3.4). The SF-36 summary was split into mental and physical components. The mental component scores were similar between the groups, with a mean change from baseline at week 24 of 6.22 for the SC group and 6.54 for the IV group. The physical component scores were also similar between the groups, with mean change from baseline at week 24 of 9.49 for the SC group and 9.65 for the IV group.

***Laboratory Evaluations***

Treatment with 8 mg/kg tocilizumab in combination with DMARD/MTX or as monotherapy resulted in a highly statistically significant improvement in haemoglobin levels compared with placebo + MTX/DMARD ($p<0.0001$) at week 24. The greatest improvement was observed in patients with chronic anaemia associated with RA; mean haemoglobin levels increased by week 2 and remained within normal range through week 24.

A marked decrease in mean levels of acute phase reactants, CRP, ESR, and serum amyloid A occurred rapidly after tocilizumab administration. Consistent with the effect on acute phase reactants, treatment with tocilizumab was associated with reduction in platelet count within the normal range

## Giant Cell Arteritis (GCA)

Study WA28119 was a randomized, multi-center, double-blind placebo-controlled Phase III superiority study conducted to assess the efficacy and safety of tocilizumab in patients with GCA.

Two hundred and fifty one (251) patients with new-onset or relapsing GCA were enrolled and assigned to one of four treatment arms. The study consisted of a 52-week blinded period (Part 1), followed by a 104-week open-label extension (Part 2). The purpose of the Part 2 is to describe the long-term safety and maintenance of efficacy after 52 weeks of tocilizumab therapy, to explore the rate of relapse and the requirement for tocilizumab therapy beyond 52 weeks, and to gain insight into the potential long-term steroid-sparing effect of tocilizumab.

Two subcutaneous (SC) doses of tocilizumab (162 mg every week and 162 mg every other week) were compared to two different placebo control groups randomized 2:1:1:1.

All patients received background glucocorticoid (prednisone) therapy. Each of the tocilizumab-treated groups and one of the placebo-treated groups followed a pre-specified prednisone-taper regimen over 26 weeks, while the second placebo treated group followed a pre-specified prednisone-taper regimen over 52 weeks designed to be more in keeping with standard practice.

The primary efficacy endpoint, assessed by the proportion of patients achieving steroid-free sustained remission at Week 52 on tocilizumab plus 26 weeks prednisone taper compared with placebo plus 26 weeks prednisone taper, was met (Table 2).
The key secondary efficacy endpoint, also based on the proportion of patients achieving sustained remission at Week 52, comparing tocilizumab plus 26 weeks prednisone taper with the longer placebo plus 52 weeks prednisone taper, was also met (Table 2).

A statistically significant superior treatment effect was seen in favour of tocilizumab over placebo in achieving steroid-free sustained remission at Week 52 on tocilizumab plus 26 weeks prednisone taper compared with placebo plus 26 weeks prednisone taper and with placebo plus 52 weeks prednisone taper.

The percentage of patients achieving sustained remission at week 52 are shown in Table 2 below.

*Secondary Endpoints*

The assessment of the time to first GCA flare showed a significantly lower risk of flare for the tocilizumab SC weekly group compared to placebo plus 26 weeks prednisone and placebo plus 52 weeks prednisone taper groups and for the tocilizumab SC every other weekly group compared to placebo plus 26 weeks prednisone (when compared at a 0.01 significance level). Tocilizumab SC weekly dose also showed a clinically meaningful decrease in the risk for flare compared to placebo plus 26 weeks prednisone in patients who entered the trial with relapsing GCA as well as those with new-onset disease (Table 2).

*Cumulative glucocorticoid dose*

The cumulative prednisone dose at Week 52 was significantly lower in the two tocilizumab dose groups compared to the two placebo groups (Table 2). In a separate analysis of the patients who received escape prednisone to treat GCA flare during the first 52 weeks, the cumulative prednisone dose varied greatly. The median doses for escape patients in the tocilizumab weekly and every other weekly groups were 3129.75 mg and 3847 mg, respectively – both considerably lower than in the placebo plus 26 weeks and the placebo plus 52 weeks prednisone taper groups, 4023.5 mg and 5389.5 mg respectively.

## Table 3: Efficacy Results from Study WA28119

| | PBO + 26 weeks prednisone taper N=50 | PBO + 52 weeks prednisone taper N=51 | TCZ 162mg SC QW + 26 weeks prednisone taper N=100 | TCZ 162 mg SC Q2W + 26 weeks prednisone taper N=49 |
|---|---|---|---|---|
| **Primary Endpoint** | | | | |
| Sustained remission (TCZ groups vs PBO+26) | | | | |
| Responders at Week 52, n (%) | 7 (14%) | 9 (17.6%) | 56 (56%) | 26 (53.1%) |
| Unadjusted difference in proportions | N/A | N/A | 42%* | 39.06%* |
| (99.5% CI) | | | (18.00, 66.00) | (12.46 , 65.66) |
| **Key Secondary Endpoint** | | | | |
| Sustained remission (TCZ groups vs PBO+52) | | | | |
| Responders at Week 52, n (%) | 7 (14%) | 9 (17.6%) | 56 (56%) | 26 (53.1%) |
| Unadjusted difference in proportions | N/A | N/A | 38.35%* | 35.41%** |
| (99.5% CI) | | | (17.89 , 58.81) | (10.41 ,60.41) |
| **Other Secondary Endpoints** | | | | |
| Time to first GCA flare[1] (TCZ groups vs PBO+26) | N/A | N/A | 0.23* | 0.28** |
| HR (99% CI) | | | (0.11, 0.46) | (0.12, 0.66) |
| Time to first GCA flare[1] (TCZ groups vs PBO+52) | N/A | N/A | 0.39** | 0.48 |
| HR (99% CI) | | | (0.18, 0.82) | (0.20, 1.16) |
| Time to first GCA flare[1] (Relapsing patients; TCZ groups vs PBO +26) HR (99% CI) | N/A | N/A | 0.23*** | 0.42 |
| | | | (0.09,0.61) | (0.14, 1.28) |
| Time to first GCA flare[1] (Relapsing patients; TCZ groups vs PBO + 52) HR (99% CI) | N/A | N/A | 0.36 | 0.67 |
| | | | (0.13, 1.00) | (0.21,2.10) |
| Time to first GCA flare[1] (New-onset patients; TCZ groups vs PBO +26) HR (99% CI) | N/A | N/A | 0.25*** | 0.20*** |
| | | | (0.09, 0.70) | (0.05, 0.76) |
| Time to first GCA flare[1] (New-onset patients; TCZ groups vs PBO + 52) HR (99% CI) | N/A | N/A | 0.44 | 0.35 |
| | | | (0.14, 1.32) | (0.09, 1.42) |
| Cumulative glucocorticoid dose (mg) | | | | |
| median at Week 52 (TCZ groups vs PBO+26[2]) | 3296.00 | N/A | 1862.00* | 1862.00** |
| median at Week 52 (TCZ groups vs PBO +52[2]) | N/A | 3817.50 | 1862.00* | 1862.00* |
| **Exploratory Endpoints** | | | | |
| Annualized relapse rate, Week 52[§] | 1.74 | 1.30 | 0.41 | 0.67 |
| Mean (SD) | (2.18) | (1.84) | (0.78) | (1.10) |

* p<0.0001
** p<0.005 (threshold for significance for primary and key secondary tests of superiority)
*** descriptive p value <0.005
[1] analysis of the time (in days) between clinical remission and first disease flare
[2] p-values are determined using a Van Elteren analysis for non-parametric data

§ statistical analyses has not been performed
N/A= Not applicable
HR = Hazard Ratio; CI = Confidence Interval
TCZ: Tocilizumab
PBO: Placebo
QW: every week dose
Q2W: every other week dose

*Quality of Life Outcomes*

In study WA28119, the SF-36 results were separated into the physical and mental component summary scores (PCS and MCS, respectively). The PCS mean change from baseline to week 52 was higher (showing more improvement) in the tocilizumab weekly and every other weekly dose groups [4.10, 2.76, respectively] than in the two placebo (PBO) groups [PBO plus 26 weeks; -0.28, PBO plus 52 weeks; -1.49], although only the comparison between tocilizumab weekly plus 26 weeks prednisone taper group and placebo plus 52 weeks prednisone taper group (5.59, 99% CI: 0.86 10.32) showed a statistically significant difference (p=0.0024). For MCS, the mean change from baseline to week 52 for both tocilizumab weekly and every other weekly dose groups [7.28, 6.12, respectively] were higher than the placebo plus 52 weeks prednisone taper group [2.84] (although the differences were not statistically significant [p=0.0252 for weekly, p=0.1468 for every other weekly]) and similar to the placebo plus 26 weeks prednisone taper group [6.67].

The Patient's Global Assessment of disease activity was assessed on a 0- 100mm Visual Analogue Scale (VAS). The mean change in Patient's global VAS from baseline at week 52 was lower (showing greater improvement) in the tocilizumab weekly and every other weekly dose groups [-19.0, -25.3, respectively] than in both placebo groups [PBO plus 26 weeks; -3.4, PBO plus 52 weeks; -7.2], although only the tocilizumab every other weekly plus 26 weeks prednisone taper group showed a statistically significance difference compared to placebo [PBO plus 26 weeks taper p=0.0059, and PBO plus 52 week taper p=0.0081].

FACIT-Fatigue change from baseline to Week 52 scores were calculated for all groups. The mean [SD] change scores were as follows: tocilizumab weekly plus 26 weeks 5.61 [10.115], tocilizumab every other weekly plus 26 weeks 1.81 [8.836], PBO plus 26 weeks 0.26 [10.702], and PBO plus 52 weeks -1.63 [6.753]. Change in EQ5D scores from baseline to week 52 were tocilizumab weekly plus 26 weeks 0.10 [0.198], tocilizumab every other weekly plus 26 weeks 0.05 [0.215], PBO plus 26 weeks 0.07 [0.293], and PBO plus 52 weeks -0.02 [0.159].

Higher scores signal improvement in both FACIT-Fatigue and EQ5D.

## 3.2 Pharmacokinetics Properties

Pharmacokinetics (PK) of tocilizumab is characterized by nonlinear elimination which is a combination of linear clearance and Michaelis-Menten elimination. The nonlinear 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. Due to the dependence of total clearance on tocilizumab serum concentrations, the half-life of tocilizumab is also concentration-dependent and varies depending on the serum concentration level. Population pharmacokinetic analyses in any patient population tested so far indicate no relationship between apparent clearance and the presence of anti-drug antibodies.

**Rheumatoid Arthritis**
The pharmacokinetics in healthy subjects and RA patients suggest that PK is similar between the two populations.

The table below shows model predicted secondary PK parameters at each of the four approved dose regimens. The population PK (popPK) model was developed from an analysis dataset composed of an IV dataset of 1793 patients from studies WA17822, WA17824, WA18062 and WA18063 and IV and SC dataset of 1759 patients from studies WA22762 and NA25220. $C_{mean}$ is included in the table since for dosing regimens with different inter-dose interval, the mean concentration over the dosing period characterizes the comparative exposure better than $AUC_{\tau}$.

**Table 4: Predicted mean ± SD PK parameters at steady-state after IV and SC dosing in RA**

| | **IV** | | **SC** | |
|---|---|---|---|---|
| **TCZ PK Parameter** | **4 mg/kg Q4W** | **8 mg/kg Q4W** | **162 mg Q2W** | **162 mg QW** |
| $C_{max}$ (mcg/mL) | 83.8 ± 23.1 | 182 ± 50.4 | 13.2 ± 8.8 | 49.8 ± 21.0 |
| $C_{trough}$ (mcg/mL) | 0.5 ± 1.5 | 15.9 ± 13.1 | 5.7 ± 6.8 | 43.0 ± 19.8 |
| $C_{mean}$ (mcg/mL) | 17.8 ± 6.1 | 56.6 ± 19.3 | 10.2 ± 8.0 | 47.4 ± 20.5 |
| | | | | |
| Accumulation $C_{max}$ | 1.01 | 1.09 | 2.12 | 5.27 |
| Accumulation $C_{trough}$ | 2.62 | 2.47 | 6.02 | 6.30 |
| Accumulation $C_{mean}$ or AUCτ * | 1.09 | 1.32 | 2.67 | 6.32 |

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

At high serum concentrations, when total clearance of tocilizumab is dominated by linear clearance, a terminal half-life of approximately 21.5 days was derived from the population parameter estimates.

Exposures after the 162 mg SC QW regimen were greater by 4.6 ($C_{mean}$) to 7.5 fold ($C_{trough}$) compared to the 162 SC Q2W regimen.

Accumulation ratios after multiple doses of either SC regimen were higher with the highest ratios for $C_{trough}$ (6.02 and 6.30). The higher accumulation for $C_{trough}$ was expected based on the nonlinear clearance contribution at lower concentrations.

For $C_{max}$, more than 90% of the steady-state was reached after the $12^{th}$ SC and the $5^{th}$ SC injection in QW and Q2W regimens respectively. For AUCτ and $C_{mean}$, 90% of the steady-state was reached after the $6^{th}$ and $12^{th}$ injections for the 162 mg SC Q2W and QW regimens respectively. For $C_{trough}$, approximately 90% of the steady-state was reached after the $6^{th}$ and $12^{th}$ injections for the respective SC regimens.

Due to the flat dosing employed for SC administration of tocilizumab, no modifications are necessary by this dosing route.

**Giant Cell Arteritis (GCA)**

The pharmacokinetics of tocilizumab in GCA patients were determined using a popPK model from an analysis dataset composed of 149 GCA patients treated with 162 mg SC every week or with 162 mg SC every other week. The developed model had the same structure as the population PK model developed earlier based on data from RA patients.

**Table 5 : Predicted mean ± SD PK parameters at steady-state after SC dosing in GCA**

| | SC | |
|---|---|---|
| **TCZ PK Parameter** | **162 mg Q2W** | **162 mg QW** |
| $C_{max}$ (mcg/mL) | 19.3 ± 12.8 | 73 ± 30.4 |
| $C_{trough}$ (mcg/mL) | 11.1 ± 10.3 | 68.1 ± 29.5 |
| $C_{mean}$ (mcg/mL) | 16.2 ± 11.8 | 71.3 ± 30.1 |
| Accumulation $C_{max}$ | 2.26 | 8.88 |
| Accumulation $C_{trough}$ | 5.61 | 9.59 |
| Accumulation $C_{mean}$ or $AUC_{\tau}$ * | 2.81 | 10.91 |

$_{\tau}$ *= 2 week or 1 week for the two SC regimens, respectively

The steady-state profile following the tocilizumab weekly dose was almost flat, with very little fluctuations between trough and peak values, while there were substantial fluctuations for the tocilizumab every other week dose. Approximately 90% of the steady-state (AUCτ) was reached by Week 14 in the every other weekly and Week 17 in the weekly dose groups.

### 3.2.1 Absorption

Following SC dosing in RA and GCA patients, the absorption half-life was around 4 days. The bioavailability for the SC formulation was 80%.

In GCA patients, the median values of $T_{max}$ were 3 days after the tocilizumab weekly dose and 4.5 days after the tocilizumab every other week dose.

### 3.2.2 Distribution

In GCA patients, the central volume of distribution was 4.09 L, the peripheral volume of distribution was 3.37 L resulting in a volume of distribution at stead state of 7.46 L.

### 3.2.3 Metabolism

*No text.*

### 3.2.4 Elimination

The total clearance of tocilizumab was concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 12.5 mL/h in RA patients, 6.7 mL/h in RA patients, 5.8 mL/h in paediatric patients with polyarticular juvenile idiopathic arthritis and 5.7 mL/h in paediatric patients with systemic juvenile idiopathic arthritis. The concentration-dependent nonlinear clearance plays a major role at low tocilizumab concentrations. Once the nonlinear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance. Due to dependence of total clearance on tocilizumab serum concentrations, $t_{1/2}$ of tocilizumab is also concentration dependent and can only be calculated at a given serum concentration level.

In RA patients, for subcutaneous administration, the concentration-dependent apparent $t_{1/2}$ is up to 13 days for 162 mg every week and 5 days for 162 mg every other week in patients with RA at steady-state. At high serum concentrations, when total clearance of tocilizumab is dominated by linear clearance, a terminal $t_{1/2}$ of approximately 21.5 days was derived from the population parameter estimates.

In GCA patients, at steady state, the effective t1/2 of tocilizumab varied between 18.3 and 18.9 days for 162 mg weekly regimen, and between 4.2 and 7.9 days for 162 mg every other weekly regimen. At high serum concentrations, when total clearance of tocilizumab is dominated by linear clearance, an effective $t_{1/2}$ of approximately 32 days was derived from the population parameter estimates.

### 3.2.5. Pharmacokinetics in Special Populations

*Hepatic Impairment*
No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab was conducted.

*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 GCA 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 the pharmacokinetics of tocilizumab.

Approximately one-third of the patients in the study WA28119 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.

*Other special populations*
Population pharmacokinetic analyses in GCA patients showed that age, sex and race did not affect pharmacokinetics of tocilizumab. No dose adjustment is necessary for these demographic factors.

## 3.3 Nonclinical Safety

### 3.3.1 Carcinogenicity
A carcinogenicity study of tocilizumab has not been conducted. Available preclinical data, showed the contribution of the pleiotropic cytokine IL-6 to malignant progression and apoptosis resistance of various cancer types. These data do not suggest a relevant risk for cancer initiation and progression under therapy with tocilizumab. Accordingly, proliferate lesions have not been observed in a chronic cynomolgus monkey 6-month toxicity study nor were they described in IL-6 knock-out mice under chronic IL-6 depletion.

### 3.3.2 Genotoxicity
Standard genotoxicity studies with tocilizumab in both prokaryotic and eukaryotic cells were all negative.

### 3.3.3 Impairment of Fertility
Nonclinical data do not suggest an effect on fertility under treatment with an analogue of tocilizumab. Effects on endocrine active organs or on organs of the reproductive system were not seen in a chronic cynomolgus monkey toxicity study, nor was the reproductive performance affected in IL-6 deficient male and female mice.

### 3.3.4 Reproductive Toxicity

When tocilizumab was administered intravenously to cynomolgus monkeys during early gestation, no direct or indirect harmful effects on pregnancy or embryo-foetal development were observed.

### 3.3.5 Other

In an embryo-foetal toxicity study conducted in cynomolgus monkeys a slight increase of abortion/embryo-foetal death was observed with high systemic cumulative exposure (above 100 times human exposure) in the 50 mg/kg/day high-dose group compared to placebo and other low-dose groups. The abortion incidence was within the historical background for the cynomolgus monkey in captivity and the individual cases of abortions/embryo-foetal death did not show any consistent relationship to dosing or duration of dosing with tocilizumab. Although IL-6 does not seem to be a critical cytokine for either foetal growth or the immunological control of the maternal/foetal interface, a relation of this finding to tocilizumab cannot be excluded.

Transfer of a murine analogue of tocilizumab into the milk of lactating mice has been observed.

Treatment with a murine analogue did not exert toxicity in juvenile mice. In particular, there was no impairment of skeletal growth, immune function and sexual maturation.

The non-clinical safety profile of tocilizumab in the cynomolgus monkey does not suggest a difference between IV and SC routes of administration.

## 4. PHARMACEUTICAL PARTICULARS

### 4.1 Storage

*Subcutaneous tocilizumab:*

The medicine should not be used after the expiry date shown on the PFS, and the pack. Store the PFS in a refrigerator at a temperature of 2-8°C. Do not freeze, keep in carton to protect from light, and keep dry.

### 4.2 Special Instructions for Use, Handling and Disposal

*Subcutaneous tocilizumab:*

Do not use if the medicine is cloudy or contains particles, is any colour besides colourless to yellowish, or any part of the PFS+NSD appears to be damaged.

Disposal of syringes/sharps:

The following points should be strictly adhered to regarding the use and disposal of the PFS+NSD:

- Syringes should never be reused.
- Place all used syringes into a sharps container (puncture-proof disposable container).
- Keep this 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 syringes.

*Disposal of unused/expired medicines*
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater, and disposal through household waste should be avoided. Use established '*collection systems*' if available in your location.

### 4.3 Shelf Life

24 months when stored at recommended storage conditions.

### 4.4 Pack Size

| *Presentation* | *Pack size* |
|---|---|
| PFS+NSD | 4 |
| PFS+NSD | 1 |

### 4.5 Incompatibilities

No text

## 5 DESCRIPTION

Tocilizumab is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass with a typical H2L2 polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The four polypeptide chains are linked intra and inter-molecularly by disulfide bonds. Actemra has a molecular weight of approximately 148 kDa. The antibody is produced in mammalian (Chinese hamster ovary) cells.

***Subcutaneous Injection***

Tocilizumab solution for subcutaneous (SC) injection is a yellowish, preservative free liquid supplied in a ready-to-use, single-use pre-filled syringe with needle safety device (PFS+NSD). Each 1mL prefilled syringe contains Tocilizumab 180 mg (162mg/0.9mL), Polysorbate 80 , L-arginine , L-arginine hydrochloride , L-methionine , L-histidine , L-histidine hydrochloride monohydrate , and Water for Injection.

# 6 PATIENT COUNSELING INFORMATION

## Patient Counseling

### Infections

Inform patients that Actemra may lower their resistance to infections. Instruct the patient of the importance of contacting their doctor immediately when symptoms suggesting infection appear in order to assure rapid evaluation and appropriate treatment.

### Gastrointestinal Perforation

Inform patients that some patients who have been treated with Actemra have had serious side effects in the stomach and intestines. Instruct the patient of the importance of contacting their doctor immediately when symptoms of severe, persistent abdominal pain appear to assure rapid evaluation and appropriate treatment.

### Hypersensitivity and Serious Allergic Reactions

Assess patient suitability for home use for subcutaneous injection. Inform patients that some patients who have been treated with Actemra have developed serious allergic reactions, including anaphylaxis.

Advise patients to seek immediate medical attention if they experience any symptom of serious allergic reactions.

### Instruction on Injection Technique

Perform the first injection under the supervision of a qualified healthcare professional. If a patient or caregiver is to administer subcutaneous Actemra, instruct him/her in injection techniques and assess his/her ability to inject subcutaneously to ensure proper administration of subcutaneous Actemra and the suitability for home use.

Prior to use, remove the prefilled syringe (PFS) from the refrigerator and allow to sit at room temperature outside of the carton for 30 minutes (PFS) out of the reach of children. Do not warm Actemra in any other way.

Advise patients to consult their healthcare provider if the full dose is not received.

A puncture-resistant container for disposal of needles, syringes should be used and should be kept out of the reach of children. Instruct patients or caregivers in the technique as well as proper needle, syringe and disposal, and caution against reuse of these items.

### Pregnancy

Inform female patients of reproductive potential that Actemra may cause fetal harm and to inform their prescriber of a known or suspected pregnancy.

Keep out of reach of children

## 7 DETAILS OF MANUFACTURER

**Manufactured by**: F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, CH-4070, Basel, Switzerland at Vetter Pharma Fertigung GmbH & Co KG,Schützenstrasse 87 and 99 101, D 88212 Ravensburg, Germany

**Imported and Marketed by:**
Roche Products (India) Pvt. Ltd.,
C/O. Parekh Integrated Services Pvt. Ltd, Gala No. A1, First Floor, Warehouse no. 6, BGR Logistics Park, NH-3, Zone 5, Bhiwandi, Maharashtra (India) – 421302.

## 8 DETAILS OF PRESCRIPTION OR LICENSE NUMBER WITH DATE

Permission No. IMP/BIO/18/000029 dated 05-Dec-2018

## 9 DATE OF REVISION

Current at March 2022 , Version 7.0