

## NAME OF THE MEDICINE

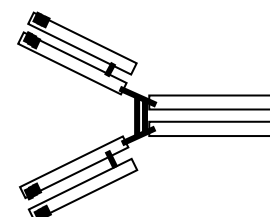
### ACTEMRA<sup>®</sup>

**Concentrated solution for intravenous infusion**

**Solution for subcutaneous injection**

*Tocilizumab (rch)*

CAS 375823-41-9



Tocilizumab is a recombinant humanised monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass which binds to human interleukin 6 (IL-6) receptors. It is composed of two heterodimers, each of which consists of a heavy and a light polypeptide chain. The light chain contains 214 amino acids and the heavy chain 448 amino acids. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. Tocilizumab has a molecular weight of approximately 148,000 Daltons. Tocilizumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R).

## DESCRIPTION

ACTEMRA concentrated solution for intravenous (IV) infusion is a clear to opalescent, colourless to pale yellow sterile solution. ACTEMRA is supplied in preservative-free, non-pyrogenic single-use, clear glass vials. ACTEMRA is available in 10 mL and 20 mL vials containing 4 mL, 10 mL or 20 mL of tocilizumab concentrate (20 mg/mL). ACTEMRA also contains polysorbate 80, sucrose, dibasic sodium phosphate dodecahydrate, monobasic sodium phosphate dihydrate and water for injections.

ACTEMRA solution for subcutaneous (SC) injection is a clear to strongly opalescent, colourless to slightly yellowish sterile solution. ACTEMRA is supplied as a preservative-free, non-pyrogenic solution presented in a ready-to-use, single-use pre-filled syringe with needle safety device. Each presentation delivers 0.9 mL (162 mg) of tocilizumab. ACTEMRA solution for SC injection also contains histidine, histidine hydrochloride, polysorbate 80, arginine, arginine hydrochloride, methionine and water for injections.

## PHARMACOLOGY

### Mechanism of Action

Tocilizumab is a recombinant humanised monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass. Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors, and has been shown to inhibit sIL-6R and mIL-6R-mediated signaling. IL-6 is a multi-functional 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 inflammatory diseases, including rheumatoid arthritis (RA).

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.

### **Pharmacodynamics**

In clinical studies with tocilizumab, rapid decreases in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and serum amyloid A were observed. Rapid increases in haemoglobin levels (within the first 2 weeks) were also observed, through tocilizumab decreasing the IL-6 driven effects on hepcidin production to increase iron availability.

In healthy subjects administered tocilizumab in doses from 2 to 28 mg/kg, absolute neutrophil counts (ANC) decreased to their lowest levels 3 to 5 days following administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. Patients with RA demonstrated a similar pattern of absolute neutrophil counts following tocilizumab administration (see PRECAUTIONS - Haematological Abnormalities).

### **Pharmacokinetics**

#### ***Rheumatoid Arthritis***

##### **Intravenous Administration**

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 1793 RA patients treated with a one hour infusion of 4 and 8 mg/kg every 4 weeks for 24 weeks.

The pharmacokinetic parameters of tocilizumab did not change with time. A more than dose-proportional increase in area under the curve (AUC) and trough concentration ( $C_{\min}$ ) was observed for doses of 4 and 8 mg/kg every 4 weeks. Maximum concentration ( $C_{\max}$ ) increased dose-proportionally. At steady-state, predicted AUC and  $C_{\min}$  were 2.7 and 6.5 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively.

The following parameters are valid for a dose of 8 mg/kg tocilizumab given every 4 weeks. Predicted mean ( $\pm$  SD) steady-state AUC,  $C_{\min}$  and  $C_{\max}$  of tocilizumab were  $35000 \pm 15500$  h· $\mu$ g/mL,  $9.74 \pm 10.5$  ng/mL, and  $183 \pm 85.6$   $\mu$ g/mL, respectively. The accumulation ratios for AUC and  $C_{\max}$  were small; 1.22 and 1.06, respectively. The accumulation ratio was higher for  $C_{\min}$  (2.35), which was expected based on the nonlinear clearance contribution at lower concentrations. Steady-state was reached following the first administration and after 8 and 20 weeks for  $C_{\max}$ , AUC, and  $C_{\min}$ , respectively. Tocilizumab AUC,  $C_{\min}$  and  $C_{\max}$  increased with increase of body weight. At body weight  $\geq 100$  kg, the predicted mean ( $\pm$  SD) steady-state AUC,  $C_{\min}$  and  $C_{\max}$  of tocilizumab were  $55500 \pm 14100$  h· $\mu$ g/mL,  $19.0 \pm 12.0$  ng/mL, and  $269 \pm 57$  ng/mL, respectively, which are higher than mean exposure values for the patient population. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended in patients  $\geq 100$  kg (see DOSAGE AND ADMINISTRATION).

The following parameters are valid for a dose of 4 mg/kg tocilizumab given every 4 weeks. Predicted mean ( $\pm$  SD) steady-state AUC,  $C_{\min}$  and  $C_{\max}$  of tocilizumab were  $13000 \pm 5800 \mu\text{g}\cdot\text{h}/\text{mL}$ ,  $1.49 \pm 2.13 \text{ ng}/\text{mL}$ , and  $88.3 \pm 41.4 \mu\text{g}/\text{mL}$ , respectively. The accumulation ratios for AUC and  $C_{\max}$  were small; 1.11 and 1.02, respectively. The accumulation ratio was higher for  $C_{\min}$  (1.96). Steady-state was reached following the first administration for both  $C_{\max}$  and AUC and from 16 weeks for  $C_{\min}$ .

### Subcutaneous Administration

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 1759 RA patients treated with 162 mg SC every week, 162 mg SC every other week, and 8 mg/kg every 4 weeks for 24 weeks.

The pharmacokinetic parameters of tocilizumab did not change with time. For the 162 mg SC every week dose, the predicted mean ( $\pm$  SD) steady-state  $\text{AUC}_{1\text{week}}$ ,  $C_{\min}$  and  $C_{\max}$  of tocilizumab were  $8200 \pm 3600 \text{ mcg}\cdot\text{h}/\text{mL}$ ,  $44.6 \pm 20.6 \text{ mcg}/\text{mL}$ , and  $50.9 \pm 21.8 \text{ mcg}/\text{mL}$ , respectively. The accumulation ratios for AUC,  $C_{\min}$ , and  $C_{\max}$  were 6.83, 6.37, and 5.47, respectively. Steady state was reached after 12 weeks for AUC,  $C_{\min}$ , and  $C_{\max}$ .

For the 162 mg SC every other week dose, the predicted mean ( $\pm$  SD) steady-state  $\text{AUC}_{2\text{week}}$ ,  $C_{\min}$ , and  $C_{\max}$  of tocilizumab were  $3200 \pm 2700 \text{ mcg}\cdot\text{h}/\text{mL}$ ,  $5.6 \pm 7.0 \text{ mcg}/\text{mL}$ , and  $12.3 \pm 8.7 \text{ mcg}/\text{mL}$ , respectively. The accumulation ratios for AUC,  $C_{\min}$ , and  $C_{\max}$  were 2.67, 5.6, and 2.12, respectively. Steady state was reached after 12 weeks for AUC and  $C_{\min}$ , and after 10 weeks for  $C_{\max}$ .

### ***Polyarticular Juvenile Idiopathic Arthritis***

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

The following parameters are valid for a dose of 8 mg/kg tocilizumab (patients with a body weight  $\geq 30$  kg) given every 4 weeks. The predicted mean ( $\pm$  SD)  $\text{AUC}_{4\text{weeks}}$ ,  $C_{\max}$  and  $C_{\min}$  of tocilizumab were  $29500 \pm 8660 \mu\text{g}\cdot\text{hr}/\text{mL}$ ,  $182 \pm 37 \mu\text{g}/\text{mL}$  and  $7.49 \pm 8.2 \mu\text{g}/\text{mL}$ , respectively.

The following parameters are valid for a dose of 10 mg/kg tocilizumab (patients with a body weight  $< 30$  kg) given every 4 weeks. The predicted mean ( $\pm$  SD)  $\text{AUC}_{4\text{weeks}}$ ,  $C_{\max}$  and  $C_{\min}$  of tocilizumab were  $23200 \pm 6100 \mu\text{g}\cdot\text{hr}/\text{mL}$ ,  $175 \pm 32 \mu\text{g}/\text{mL}$  and  $2.35 \pm 3.59 \mu\text{g}/\text{mL}$ , respectively.

The accumulation ratios were 1.05 and 1.16 for  $\text{AUC}_{4\text{weeks}}$ , and 1.43 and 2.22 for  $C_{\min}$  for 10 mg/kg (body weight (BW)  $< 30$  kg) and 8 mg/kg (BW  $\geq 30$  kg) doses, respectively. No accumulation for  $C_{\max}$  was observed.

### ***Systemic Juvenile Idiopathic Arthritis***

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 75 patients with systemic juvenile idiopathic arthritis (sJIA) treated with 8 mg/kg (patients with a body weight  $\geq$  30 kg) or 12 mg/kg (patients with a body weight  $<$  30 kg), given every 2 weeks. The predicted mean ( $\pm$  SD)  $AUC_{2weeks}$ ,  $C_{max}$  and  $C_{min}$  of tocilizumab were  $32200 \pm 9960 \mu\text{g}\cdot\text{hr}/\text{mL}$ ,  $245 \pm 57.2 \mu\text{g}/\text{mL}$  and  $57.5 \pm 23.3 \mu\text{g}/\text{mL}$ , respectively. The accumulation ratio for  $C_{min}$  (week12/week2) was  $3.2 \pm 1.3$ . The tocilizumab  $C_{min}$  was stabilised after week 12. Mean predicted tocilizumab exposure parameters were similar between the two body weight groups.

### ***Absorption***

Following SC dosing in RA patients, the absorption half-life was around 4 days. The bioavailability for the SC formulation was 0.8.

### ***Distribution***

Following IV dosing, tocilizumab undergoes biphasic elimination from the circulation. In RA patients the central volume of distribution was 3.5 L and the peripheral volume of distribution was 2.9 L, resulting in a volume of distribution at steady state of 6.4 L.

In paediatric patients with pJIA, the central volume of distribution was 1.98 L, the peripheral volume of distribution was 2.1 L, resulting in a volume of distribution at steady state of 4.08 L.

In paediatric patients with sJIA, the central volume of distribution was 0.94 L and the peripheral volume of distribution was 1.60 L resulting in a volume of distribution at steady state of 2.54 L.

### ***Metabolism***

Not applicable.

### ***Excretion***

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, 5.8 mL/h in paediatric patients with pJIA and 7.1 mL/h in paediatric patients with sJIA. 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.

The half-life ( $t_{1/2}$ ) of tocilizumab is concentration-dependent in RA. For intravenous administration, the concentration-dependent apparent  $t_{1/2}$  is up to 11 days for 4 mg/kg and 13 days for 8 mg/kg every 4 weeks in patients with RA at steady-state. 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.

The  $t_{1/2}$  of tocilizumab in children with pJIA is up to 16 days for the two body weight categories (8 mg/kg for BW  $\geq$  30 kg or 10 mg/kg for BW < 30 kg) during a dosing interval at steady state.

The  $t_{1/2}$  of tocilizumab in children with sJIA is up to 23 days for the two body weight categories (8 mg/kg for body weight  $\geq$  30 kg or 12 mg/kg for body weight < 30 kg) at week 12.

### ***Pharmacokinetics in Special Populations***

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

*Renal Impairment:* No formal study of the effect of renal impairment on the pharmacokinetics of ACTEMRA was conducted.

Most of the patients in the RA population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (creatinine clearance based on Cockcroft-Gault < 80 mL/min and <sup>3</sup> 50 mL/min) did not impact the pharmacokinetics of ACTEMRA. ACTEMRA has not been studied in patients with moderate to severe renal impairment. (See CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

*Other special populations:* Population pharmacokinetics in adult RA patients showed that age, gender and race did not affect the pharmacokinetics of ACTEMRA. No dose adjustment is necessary for these demographic factors.

## **CLINICAL TRIALS**

### **Rheumatoid Arthritis**

The efficacy of intravenous ACTEMRA in alleviating the signs and symptoms of RA was assessed in five randomised, double-blind, multicentre studies (Studies I – V). The efficacy of subcutaneous ACTEMRA was assessed in two randomised, double-blind studies (Studies VI and VII). In addition, the efficacy of intravenous ACTEMRA has been evaluated in patients with MTX-naïve, early RA (Study VIII) and as a monotherapy versus adalimumab monotherapy (Study IX).

Studies I-V required patients  $\geq$  age 18 with active RA diagnosed according to American College of Rheumatology (ACR) criteria who had at least 8 tender and 6 swollen joints at baseline.

ACTEMRA was administered intravenously every 4 weeks as monotherapy (Study I), in combination with methotrexate (MTX) (Studies II, III, V) or with other disease-modifying anti-rheumatic drugs (DMARDs) (Study IV).

Study I (AMBITION) evaluated 673 patients who had not been treated with MTX within 6 months prior to randomisation, and who had not discontinued previous MTX treatment as a result of clinically important toxic effects or lack of response. The majority (67%) of patients were MTX naïve. Doses of 8 mg/kg of ACTEMRA were given every 4 weeks as monotherapy. The comparator group was weekly MTX (dose titrated from 7.5 to a

maximum of 20 mg weekly over an 8 week period). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Study II (LITHE), a 2 year study, evaluated 1196 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of ACTEMRA or placebo were given every 4 weeks as blinded therapy for 52 weeks, in combination with stable MTX (10–25 mg weekly). The primary endpoint at week 24 was the proportion of patients who achieved ACR20 response criteria. At week 52 the co-primary endpoints were prevention of joint damage and improvement in physical function.

Study III (OPTION) evaluated 623 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of ACTEMRA or placebo were given every 4 weeks, in combination with stable MTX (10 – 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Study IV (TOWARD) evaluated 1220 patients who had an inadequate response to their existing rheumatologic therapy, including one or more DMARDs. Doses of 8 mg/kg ACTEMRA or placebo were given every 4 weeks, in combination with the stable DMARD. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Study V (RADIATE) evaluated 499 patients who had an inadequate clinical response or were intolerant to one or more anti-tumour necrosis factor (TNF) therapies. The anti-TNF agent was discontinued prior to randomisation. Doses of 4 or 8 mg/kg of ACTEMRA or placebo were given every 4 weeks, in combination with stable MTX (10 – 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

The efficacy and safety of subcutaneously administered ACTEMRA was assessed in two double-blind, controlled, multicentre studies in patients with active RA.

Study VI (SUMMACTA) was a non-inferiority study that compared the efficacy and safety of subcutaneous ACTEMRA 162 mg administered every week to intravenous ACTEMRA 8 mg/kg every 4 weeks. In SUMMACTA, 1262 patients were randomised 1:1 to receive subcutaneous ACTEMRA 162 mg every week or intravenous ACTEMRA 8 mg/kg every 4 weeks in combination with DMARD(s).

Study VII (BREVACTA) was a placebo-controlled superiority study that evaluated the safety and efficacy of subcutaneous ACTEMRA 162 mg administered every other week to placebo. In BREVACTA, 656 patients were randomised 2:1 to subcutaneous ACTEMRA 162 mg every other week or placebo, in combination with DMARD(s).

The primary endpoint in both studies was the proportion of patients who achieved an ACR20 response at Week 24. Both SUMMACTA and BREVACTA required patients to be  $\geq 18$  years of age with moderate to severe active RA diagnosed according to ACR criteria. Patients had at least 4 tender and 4 swollen joints at baseline (SUMMACTA) or at least 8 tender and 6 swollen joints at baseline (BREVACTA), and an inadequate

response to their existing DMARD therapy. Approximately 20% also had a history of inadequate response to at least one TNF inhibitor. All patients in both SC studies received background non-biological DMARD(s).

The percent of patients achieving ACR 20, 50 and 70 responses in Studies I to V are shown in Table 1.

**Table 1 ACR Responses in MTX/Placebo-Controlled Trials (Percent of Patients)**

| Response Rate                       | Study I<br>MTX-Naïve    |              | Study II<br>Inadequate<br>Response to<br>MTX |                           | Study III<br>Inadequate<br>Response to<br>MTX |                           | Study IV<br>Inadequate<br>Response to<br>DMARD |                                | Study V<br>Inadequate<br>Response to<br>anti-TNF Agent |                           |
|-------------------------------------|-------------------------|--------------|--|---------------------------|---|---------------------------|--|--------------------------------|--|---------------------------|
|                                     | ACT<br>8 mg/kg<br>n=286 | MTX<br>n=284 | ACT<br>8 mg/kg<br>+MTX<br>n=398              | Placebo<br>+ MTX<br>n=393 | ACT<br>8 mg/kg<br>+MTX<br>n=205               | Placebo<br>+ MTX<br>n=204 | ACT<br>8 mg/kg<br>+<br>DMARD<br>n=803          | Placebo<br>+<br>DMARD<br>n=413 | ACT<br>8 mg/kg<br>+MTX<br>n=170                        | Placebo<br>+ MTX<br>n=158 |
| <b>ACR 20</b>                       |                         |              |  |                           |   |                           |  |                                |  |                           |
| Week 24                             | 70%***                  | 52%          | 56%***                                       | 27%                       | 59%***  | 26%                       | 61%***   | 24%                            | 50%***   | 10%                       |
| Week 52 <sup>^</sup>                |                         |              | 56%***                                       | 25%                       |   |                           |  |                                |  |                           |
| <b>ACR 50</b>                       |                         |              |  |                           |   |                           |  |                                |  |                           |
| Week 24                             | 44%**                   | 33%          | 32%***                                       | 10%                       | 44%***  | 11%                       | 38%***   | 9%                             | 29%***   | 4%                        |
| Week 52 <sup>^</sup>                |                         |              | 36%***                                       | 10%                       |   |                           |  |                                |  |                           |
| <b>ACR 70</b>                       |                         |              |  |                           |   |                           |  |                                |  |                           |
| Week 24                             | 28%**                   | 15%          | 13%***                                       | 2%                        | 22%***  | 2%                        | 21%***   | 3%                             | 12%**  | 1%                        |
| Week 52 <sup>^</sup>                |                         |              | 20%***                                       | 4%                        |   |                           |  |                                |  |                           |
| MCR †<br>by Week<br>52 <sup>^</sup> |                         |              | 7%   | 1%                        |   |                           |  |                                |  |                           |

ACT = ACTEMRA

\* p < 0.05, ACTEMRA vs. placebo + MTX/DMARD

\*\* p < 0.01, ACTEMRA vs. placebo + MTX/DMARD

\*\*\* p < 0.0001, ACTEMRA vs. placebo + MTX/DMARD

† MCR = major clinical response, defined as an ACR70 response maintained for any 24 consecutive weeks or more. Note: the comparison for MCR occurred after the break in the hierarchical ordered testing sequence, so no significance claims can be made. Secondary efficacy endpoints were tested in a fixed sequence approach in order to control for the rate of false positive conclusions.

<sup>^</sup> - based on a protocol-specified interim analysis

In studies I to V, 8 mg/kg ACTEMRA-treated patients had statistically significant higher ACR20, 50, 70 response rates at 6 months compared to placebo. The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race, number of prior treatments or disease status. Time to onset was rapid (as early as week 2) and the magnitude of response continued to improve with duration of treatment. Continued

lasting responses were seen for over 3 years in the on going open label extension studies of studies I -V.

In the 8 mg/kg ACTEMRA-treated patients significant improvements were noted on all individual components of the ACR response: tender and swollen joint counts; pain assessment and CRP normalisation; disability index scores; patients and physician global assessment, compared to patients receiving placebo + MTX/DMARDs in all studies. ACTEMRA 8 mg/kg treated patients had a statistically significant greater reduction in disease activity score (DAS28) than patients treated with placebo + DMARD. The rate of remission (defined as DAS < 2.6) for patients treated with ACTEMRA ranged from 27.5% to 33.6%. ACTEMRA treated patients had a statistically significant greater rate of remission than patients treated with placebo + DMARD. A good to moderate EULAR response was achieved by significantly more ACTEMRA treated patients compared to patients treated with placebo + DMARD (Table 2).

**Table 2 Cross-Study Comparison of DAS and EULAR Responses at Week 24**

|  | Study I<br>MTX Naïve        |                  | Study II<br>Inadequate<br>Response to MTX |                               | Study III<br>Inadequate<br>Response to MTX |                               | Study IV<br>Inadequate Response<br>to DMARD |                                    | Study V<br>Inadequate<br>Response to anti-<br>TNF Agent |                              |
|--|-----------------------------|------------------|---|-------------------------------|--|-------------------------------|---|------------------------------------|---|------------------------------|
|  | ACT<br>8 mg/kg<br><br>n=286 | MTX<br><br>n=284 | ACT<br>8 mg/kg<br>+MTX<br><br>n=398       | Placebo<br>+ MTX<br><br>n=393 | ACT<br>8 mg/kg<br>+MTX<br><br>n=205        | Placebo<br>+ MTX<br><br>n=204 | ACT<br>8 mg/kg<br>+ DMARD<br><br>n=803      | Placebo<br>+<br>DMARD<br><br>n=413 | ACT<br>8 mg/kg<br>+MTX<br><br>n=170                     | Placebo<br>+MTX<br><br>n=158 |
| <b>Change in DAS28 [mean (Adjusted mean (SE))]</b> |                             |                  |   |                               |  |                               |   |                                    |   |                              |
| Week 24  | -3.31<br>(0.12)             | -2.05<br>(0.12)  | -3.11<br>(0.09)***                        | -1.45<br>(0.11)               | -3.43<br>(0.12)***                         | -1.55<br>(0.15)               | -3.17<br>(0.07)***                          | -1.16<br>(0.09)                    | -3.16<br>(0.14)<br>***                                  | -0.95<br>(0.22)              |
| <b>DAS &lt; 2.6 response (%)</b>                   |                             |                  |   |                               |  |                               |   |                                    |   |                              |
| Week 24  | 33.6%                       | 12.1%            | 33.3%<br>***                              | ^3.8%                         | 27.5%***                                   | 0.8%                          | 30.2%***                                    | 3.4%                               | 30.1%<br>***  | 1.6%                         |
| <b>EULAR response (%)</b>                          |                             |                  |   |                               |  |                               |   |                                    |   |                              |
| None   | 18%                         | 35%              | 26%                                       | 65%                           | 20%  | 65%                           | 20%   | 62%                                | 32%   | 84%                          |
| Moderate   | 42%                         | 48%              | 34%                                       | 29%                           | 41%  | 32%                           | 40%   | 33%                                | 31%   | 15%                          |
| Good†  | 40%                         | 17%              | 41%***                                    | 6%                            | 38%***                                     | 3%                            | 40%***                                      | 4%                                 | 37%***  | 2%                           |

ACT = ACTEMRA

†The p value compares across all the EULAR categories

\* p < 0.05, ACTEMRA vs. placebo + MTX/DMARD

\*\* p < 0.01, ACTEMRA vs. placebo + MTX/DMARD

\*\*\* p < 0.0001, ACTEMRA vs. placebo + MTX/DMARD

In study II, 47% of patients achieved a DAS28 < 2.6 at 52 weeks compared to 33% of patients at week 24.

^ In study II, 8% of patients achieved a DAS28 < 2.6 at 52 weeks compared to 4% of patients at week 24.

The clinical response to 24 weeks of subcutaneous ACTEMRA therapy is shown in Table 3. In SUMMACTA, the primary outcome measure was ACR20 at Week 24. The pre-



specified non-inferiority margin was a treatment difference of 12%. The study demonstrated non-inferiority of ACTEMRA with respect to ACR20 at Week 24; ACR50, ACR70 and DAS28 responses are also shown in Table 3. The efficacy and safety of subcutaneous ACTEMRA used as a monotherapy is supported by SUMMACTA which demonstrates, in combination with DMARD(s), the non-inferiority of ACTEMRA 162 mg SC every week to 8 mg/kg IV every 4 weeks. However, the efficacy of subcutaneous ACTEMRA administered every week as a monotherapy was not directly established in this study.

**Table 3 Clinical Response at Week 24 in Subcutaneous Trials (Percent of Patients)**

|  | Study VI (SUMMACTA) <sup>a</sup>               |  | Study VII (BREVACTA) <sup>b</sup>                    |                               |
|--|--|--|--|-------------------------------|
|  | ACT SC 162 mg every week + DMARD(s)<br>n = 558 | ACT IV 8 mg/kg every 4 weeks + DMARD(s)<br>n = 537 | ACT SC 162 mg every other week + DMARD(s)<br>n = 437 | Placebo + DMARD(s)<br>n = 219 |
| <b>ACR20</b>                           |  |  |  |                               |
| Week 24                                | 69.4%  | 73.4%  | 60.9%  | 31.5%                         |
| Weighted difference (95% CI)           | -4.0 (-9.2, 1.2)                               |  | 30 (22.0, 37.0)                                      |                               |
| <b>ACR50</b>                           |  |  |  |                               |
| Week 24                                | 47.0%  | 48.6%  | 39.8%  | 12.3%                         |
| Weighted difference (95% CI)           | -1.8 (-7.5, 4.0)                               |  | 28 (21.5, 34.4)                                      |                               |
| <b>ACR70</b>                           |  |  |  |                               |
| Week 24                                | 24.0%  | 27.9%  | 19.7%  | 5.0%                          |
| Weighted difference (95% CI)           | -3.8 (-9.0, 1.3)                               |  | 15 (9.8, 19.9)                                       |                               |
| <b>Change in DAS28 [adjusted mean]</b> |  |  |  |                               |
| Week 24                                | -3.5   | -3.5   | -3.1   | -1.7                          |
| Adjusted mean difference (95% CI)      | 0 (-0.2, 0.1)                                  |  | -1.4 (-1.7, -1.1)                                    |                               |
| <b>DAS28 &lt; 2.6 response (%)</b>     |  |  |  |                               |
| Week 24                                | 38.4%  | 36.9%  | 32.0%  | 4.0%                          |
| Weighted difference (95% CI)           | 0.9 (-5.0, 6.8)                                |  | 28.6 (22.0, 35.2)                                    |                               |

ACT = ACTEMRA

<sup>a</sup> = per protocol population

<sup>b</sup> = intent to treat population

In SUMMACTA, ACR 20, 50 and 70 response rates were comparable between the subcutaneous and intravenous ACTEMRA study arms across the three body weight categories (< 60 kg, 60 – 100 kg, ≥ 100 kg). ACR 20, 50 and 70 response rates in the heaviest weight category (≥ 100 kg) were lower compared to the other weight categories in the subcutaneous and intravenous ACTEMRA study arms. The same phenomenon of lower response rates in heavier patients (≥ 100 kg) compared to other weight categories was seen in patients receiving the subcutaneous ACTEMRA every other week regimen in BREVACTA.

### ***Major Clinical Response***

After 2 years of treatment with intravenous ACTEMRA + MTX, 14% of patients achieved a major clinical response (maintenance of an ACR70 response for 24 weeks or more).

### ***Radiographic response***

In study II (LITHE), in patients with an inadequate response to MTX, inhibition of structural joint damage was assessed radiographically and expressed as change in modified Sharp score and its components, the erosion score and joint space narrowing (JSN) score. Missing week 52 radiographic data was imputed using linear extrapolation. This was performed for any patient who had a baseline assessment and at least one post-baseline radiographic assessment. The change from baseline was then calculated using the extrapolated score. Inhibition of structural joint damage was shown with significantly less radiographic progression in patients receiving ACTEMRA compared to control (Table 4).

In the open-label extension of study II further improvement in the inhibition of progression of structural damage in ACTEMRA + MTX-treated patients was observed in the second year of treatment. Study II did not investigate the effect of ACTEMRA monotherapy on radiographic endpoints.

**Table 4 Radiographic mean changes at 52 and 104 weeks in study II (LITHE)**

|                                  | <b>ACT 8 mg/kg<br/>+ MTX<br/>[n=398]</b> | <b>Placebo + MTX<br/>(+ option of ACT from week 16)<br/>[n=393]</b> |
|----------------------------------|--|---|
| Changes from baseline to week 52 |  |   |
| n                                | 353                                      | 294   |
| Total Sharp-Genant score         | 0.25                                     | 1.17  |
| Erosion score                    | 0.15                                     | 0.76  |
| JSN score                        | 0.10                                     | 0.41  |
| Change from week 52 to week 104  |  |   |
| n                                | 353                                      | 294   |
| Total Sharp-Genant score         | 0.12                                     | 0.79  |
| Erosion score                    | 0.07                                     | 0.48  |
| JSN score                        | 0.05                                     | 0.31  |

ACT = ACTEMRA

JSN = joint space narrowing

The data presented consists of the evaluations of the baseline, week 24, week 52, week 80, week 104 and early withdrawal or escape therapy readings taken up to the week 104 visit.

Following 1 year of treatment with ACTEMRA + MTX, 83% of patients had no progression of structural damage, as defined by a change in the Total Sharp Score of zero or less, compared with 67% of placebo + MTX-treated patients. This remained consistent following 2 years of treatment (83%). Ninety three percent (93%) of patients had no progression between week 52 and week 104.

In Study VII (BREVACTA), 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 subcutaneous ACTEMRA compared with placebo; mean change from baseline in mTSS of 0.62 vs. 1.23 ( $p = 0.0149$ ; van Elteren) with an adjusted mean difference of -0.60 (-1.1, -0.1). These results are consistent with those observed in patients treated with intravenous ACTEMRA.

### *Quality of Life Outcomes*

Clinically significant improvements in disability index (HAQ-DI, Health Assessment Questionnaire Disability Index), fatigue (FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue) and improvement in both the physical (PCS, Physical Component Summary) and mental health (MCS, Mental Component Summary) domains of the SF-36 (Short Form 36) were observed in patients treated with 8 mg/kg ACTEMRA (monotherapy or combination with DMARDs) compared to patients treated with MTX/DMARDs.

At week 24, the proportion of 8 mg/kg ACTEMRA treated patients showing a clinically relevant improvement in HAQ-DI (defined as an individual total score decrease of  $> 0.25$ ), was significantly higher than among patients receiving placebo + MTX/DMARDs in all studies (Studies I to V). During the open-label period of study II the improvement in physical function has been maintained for up to 2 years.

At week 52, the mean change in HAQ-DI was -0.58 in the ACTEMRA 8 mg/kg + MTX group compared with -0.39 in the placebo + MTX group. The mean change in HAQ-DI was maintained at week 104 in the ACTEMRA 8 mg/kg + MTX group (-0.61). The percentage of ACTEMRA-treated patients showing a clinically relevant improvement in HAQ-DI ( $\geq 0.3$  units) at weeks 52 & 104 were 63% and 62%, respectively.

In Study VI (SUMMACTA), the mean decrease in HAQ-DI from baseline to week 24 was 0.6 for both subcutaneous ACTEMRA 162 mg weekly and intravenous ACTEMRA 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  $\geq 0.3$  units) was comparable in the subcutaneous ACTEMRA every week group (65.2%) versus the intravenous ACTEMRA 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. In Study VII (BREVACTA), the mean decrease in HAQ-DI from baseline to week 24 was 0.4 and 0.3, and the proportion of patients who achieved a clinically relevant improvement in HAQ-DI was 58% and 47%, for the subcutaneous ACTEMRA 162 mg every other week, and placebo treatment groups, respectively.

### ***Laboratory Evaluations***

Treatment with 8 mg/kg ACTEMRA in combination with DMARD/MTX or as monotherapy resulted in a 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 ACTEMRA administration. Consistent with the effect on acute phase reactants, treatment with ACTEMRA was associated with reduction in platelet count within the normal range.

### ***MTX naïve, Early RA***

Study VIII (FUNCTION), a 2 year study with the planned primary analysis at week 52 evaluated 1162 MTX-naïve adult patients with moderate to severe, active early RA (mean disease duration  $\leq 6$  months) and one or more indicators of poor prognosis, such as elevated inflammatory markers (e.g. ESR and/or CRP), the presence of RF and/or anti-CCP, and/or the presence of bony erosions attributable to RA. This study evaluated the efficacy of intravenous ACTEMRA 4 or 8 mg/kg every 4 weeks in combination with MTX, ACTEMRA 8 mg/kg monotherapy and MTX monotherapy in reducing the signs and symptoms and rate of progression of joint damage for 104 weeks. The primary endpoint was the proportion of patients achieving DAS28 remission ( $\text{DAS28} < 2.6$ ) at week 24. A significantly higher proportion of patients in the ACTEMRA 8 mg/kg + MTX and ACTEMRA monotherapy groups met the primary endpoint compared with MTX alone. The ACTEMRA 8 mg/kg + MTX group also showed statistically significant results across the key secondary endpoints. Numerically greater responses compared with MTX alone were observed in the ACTEMRA 8 mg/kg monotherapy group in all secondary endpoints, including radiographic endpoints (although the differences between ACTEMRA 8 mg/kg monotherapy and MTX were not statistically significant). The results from study VIII are shown in Table 5.

**Table 5 Efficacy Results for Study VIII (FUNCTION) on MTX-naïve, early RA patients**

|   |         | ACT 8 mg/kg +<br>MTX<br>n=290                    | ACT 8 mg/kg<br>+ placebo<br>n=292 | Placebo + MTX<br>n=287 |      |
|---|---------|--|-----------------------------------|------------------------|------|
| <b>Primary Endpoint</b>                                   |         |  |                                   |                        |      |
| DAS < 2.6 response (%)                                    |         |  |                                   |                        |      |
|   | Week 24 | 44.8***  | 38.7***                           | 15.0                   |      |
| <b>Key Secondary Endpoints</b>                            |         |  |                                   |                        |      |
| DAS < 2.6 response (%)                                    |         |  |                                   |                        |      |
|   | Week 52 | 49.0***  | 39.4                              | 19.5                   |      |
| ACR (%)   |         |  |                                   |                        |      |
|   | Week 24 |  |                                   |                        |      |
|   |         | ACR20  | 74.5*                             | 70.2                   | 65.2 |
|   |         | ACR50  | 56.9**                            | 47.6                   | 43.2 |
|   |         | ACR70  | 38.6**                            | 30.1                   | 25.4 |
|   | Week 52 |  |                                   |                        |      |
|   |         | ACR20  | 67.2*                             | 63.0                   | 57.1 |
|   |         | ACR50  | 55.9**                            | 49.3                   | 40.8 |
|   |         | ACR70  | 43.1**                            | 36.0                   | 28.9 |
| HAQ-DI (adjusted mean change from baseline)               |         |  |                                   |                        |      |
|   | Week 52 | -0.81*   | -0.67                             | -0.64                  |      |
| <b>Radiographic Endpoints (mean change from baseline)</b> |         |  |                                   |                        |      |
|   | Week 52 | mTSS <sup>#</sup>                                | 0.08***                           | 0.26                   | 1.14 |
|   |         | Erosion Score                                    | 0.05**                            | 0.15                   | 0.63 |
|   |         | JSN  | 0.03                              | 0.11                   | 0.51 |
|   |         | Radiographic non-progression (%)                 | 83 <sup>‡</sup>                   | 82 <sup>‡</sup>        | 73   |
|   |         | (change from baseline in mTSS <sup>#</sup> of 0) |                                   |                        |      |

All efficacy comparisons vs Placebo + MTX. \*\*\*p ≤ 0.0001; \*\*p < 0.001; \*p < 0.05;

<sup>#</sup> mTSS = modified Total Sharp score

### ***ACTEMRA versus adalimumab in monotherapy***

Study IX (ADACTA) evaluated 326 patients with RA who were intolerant of MTX or in whom continued treatment with MTX was considered inappropriate, which included patients considered to be MTX inadequate responders. Patients in the ACTEMRA arm received an intravenous (IV) infusion of ACTEMRA (8 mg/kg) every 4 weeks (q4w) and a subcutaneous (SC) placebo injection every 2 weeks (q2w). Patients in the adalimumab arm received an adalimumab SC injection (40 mg) q2w plus an IV placebo infusion q4w.

A statistically significant superior treatment effect was seen in favour of ACTEMRA over adalimumab in control of disease activity from baseline to week 24 for the primary endpoint of change in DAS28 and for all secondary endpoints (Table 6).

**Table 6 Efficacy Results for Study IX (ADACTA)**

|  | ADA + Placebo<br>(IV)<br>n = 162 | ACT + Placebo<br>(SC)<br>n = 163 | p-value <sup>(a)</sup> |
|--|----------------------------------|----------------------------------|------------------------|
| <b>Primary Endpoint - Mean Change from baseline at Week 24</b>                 |                                  |                                  |                        |
| DAS28 (adjusted mean)  | -1.8                             | -3.3                             |                        |
| Difference in adjusted mean (95% CI)   | -1.5 (-1.8, -1.1)                |                                  | <0.0001                |
| <b>Secondary Endpoints - Percentage of Responders at Week 24<sup>(b)</sup></b> |                                  |                                  |                        |
| DAS28 < 2.6, n (%)   | 18 (10.5)                        | 65 (39.9)                        | <0.0001                |
| DAS28 ≤ 3.2, n (%)   | 32 (19.8)                        | 84 (51.5)                        | <0.0001                |
| ACR20 response, n (%)  | 80 (49.4)                        | 106 (65.0)                       | 0.0038                 |
| ACR50 response, n (%)  | 45 (27.8)                        | 77 (47.2)                        | 0.0002                 |
| ACR70 response, n (%)  | 29 (17.9)                        | 53 (32.5)                        | 0.0023                 |

<sup>a</sup>p value is adjusted for region and duration of RA for all endpoints and additionally baseline value for all continuous endpoints.

<sup>b</sup>Non-responder Imputation used for missing data. Multiplicity controlled using Bonferroni-Holm Procedure

### **Polyarticular Juvenile Idiopathic Arthritis**

The efficacy of intravenous ACTEMRA was assessed in a three-part study including an open-label extension in children with moderately to severely active pJIA, who had an inadequate response to methotrexate (MTX) or inability to tolerate MTX (Study X, CHERISH). Patients had at least 6 months of active disease (mean disease duration of 4.2 ± 3.7 years), with at least 5 joints with active arthritis (swollen or limitation of movement accompanied by pain and/or tenderness) and/or at least 3 active joints having limitation of motion (mean, 20 ± 14 active joints). The patients treated had subtypes of JIA that at disease onset included Rheumatoid Factor Positive or Negative Polyarticular JIA, or Extended Oligoarticular JIA. Treatment with a stable dose of MTX was permitted but was not required during the study. Concurrent use of DMARDs other than MTX, or other biologics (e.g. TNF antagonists or T cell costimulation modulator) were not permitted in the study. Ten patients who participated in the study were less than 4 years of age.

Part I consisted of a 16 week active ACTEMRA treatment lead in period (n=188) followed by Part II, a 24 week randomised, double-blind, placebo-controlled withdrawal period (ITT n=163), followed by Part III, a 64 week open-label period. Eligible patients ≥ 30 kg received ACTEMRA at 8 mg/kg for 4 doses. Patients < 30 kg were randomised 1:1 to receive either ACTEMRA 8 mg/kg or 10 mg/kg IV every 4 weeks for 4 doses. Patients who completed Part I of the study and achieved at least a JIA ACR30 response at week 16 compared to baseline entered the blinded withdrawal period (Part II) of the study. In Part II, patients were randomised to ACTEMRA (same dose received in Part I) or placebo in a 1:1 ratio, stratified by concurrent MTX use and concurrent corticosteroid use. Each patient continued in Part II of the study until Week 40 or until the patient satisfied JIA ACR30 flare criteria (relative to Week 16) and qualified for escape.

The primary endpoint was the proportion of patients with a JIA ACR30 flare at week 40 relative to week 16. JIA ACR 30 flare was defined as 3 or more of the 6 core outcome variables worsening by at least 30% with no more than 1 of the remaining variables improving by more than 30% relative to Week 16. Forty eight percent (48.1%, 39/81) of the patients treated with placebo flared compared with 25.6% (21/82) of ACTEMRA-treated patients. These proportions were statistically significantly different (p=0.0024).

At the conclusion of Part I, JIA ACR 30/50/70/90 responses were 89.4%, 83.0%, 62.2%, and 26.1%, respectively.

During the withdrawal phase (Part II), the percentages of patients achieving JIA ACR 30, 50, and 70 responses at Week 40 relative to baseline are shown in the table below.

**Table 7 JIA ACR response rates at week 40 relative to baseline (percentages of patients)**

| <b>Response Rate</b> | <b>ACTEMRA<br/>n=82</b> | <b>Placebo<br/>n=81</b> |
|----------------------|-------------------------|-------------------------|
| JIA ACR 30           | 74.4% <sup>†</sup>      | 54.3% <sup>†</sup>      |
| JIA ACR 50           | 73.2% <sup>†</sup>      | 51.9% <sup>†</sup>      |
| JIA ACR 70           | 64.6% <sup>†</sup>      | 42.0% <sup>†</sup>      |

<sup>†</sup> p<0.001, ACTEMRA vs. placebo

A difference in the incidence of JIA ACR30 flare during Week 16 to 40 was observed between those patients who were and were not taking concurrent MTX, and those patients who had previously been exposed to a biologic DMARD or not. Irrespective of concurrent MTX or previous biologic DMARD use JIA ACR30 flare was lower for patients receiving ACTEMRA compared to placebo (Table 8).

**Table 8 Proportion of patients with a JIA ACR30 Flare at Week 40 by background MTX use at baseline or prior biologic DMARD use**

|                           | <b>placebo</b>      |                    | <b>ACTEMRA</b>      |                    |
|---------------------------|---------------------|--------------------|---------------------|--------------------|
| <b>MTX Use</b>            | <b>Yes (n = 64)</b> | <b>No (n = 17)</b> | <b>Yes (n = 67)</b> | <b>No (n = 15)</b> |
| JIA ACR30 Flare           | 25 (39.1%)          | 14 (82.4%)         | 13 (19.4%)          | 8 (53.3%)          |
| <b>Prior Biologic Use</b> | <b>Yes (n = 23)</b> | <b>No (n = 58)</b> | <b>Yes (n = 27)</b> | <b>No (n = 55)</b> |
| JIA ACR30 Flare           | 18 (78.3)           | 21 (36.2)          | 12 (44.4)           | 9 (16.4)           |

In Part III maintenance of efficacy through Week 104 was demonstrated for each of the JIA responses rates and were similar between the continuous ACTEMRA-treated subgroup and the placebo-treated patients in Part II who re-commenced ACTEMRA. For the continuous ACTEMRA group the JIA ACR30/50/70/90 response rates at Week 104 were 95.1%, 90.2%, 86.6% and 70.7%, respectively. For placebo-treated patients in Part II who re-commenced ACTEMRA JIA ACR30/50/70/90 response rates at Week 104

were 95.1%, 95.1%, 91.4%, and 66.7%, respectively. Improvement in JIA ACR core components observed at Week 40 was maintained.

### **Systemic Juvenile Idiopathic Arthritis**

The efficacy of intravenous ACTEMRA for the treatment of active sJIA was assessed in a 12-week randomised, double blind, placebo-controlled, parallel group, 2-arm study (Study XI, TENDER). Patients (treated with or without MTX) were randomised (ACTEMRA: placebo = 2:1) to one of two treatment groups. 75 patients received ACTEMRA infusions every two weeks either 8 mg/kg for patients  $\geq 30$ kg or 12 mg/kg for patients  $< 30$  kg and 37 patients were assigned to receiving placebo infusions every two weeks. Corticosteroid tapering could occur from week 6 for patients who achieved a JIA ACR70 response. After 12 weeks or at the time of escape, due to disease worsening, patients were treated in the open-label extension phase at weight appropriate dosing.

The demographic characteristics at baseline were similar between the placebo and ACTEMRA groups. Patients were evenly split between male and female, with a median age of 9 and 10 for the placebo and ACTEMRA groups, respectively. 27 patients in the study were aged between 2-5 years, 48 patients between 6-12 years and 37 patients between 13-18 years. Baseline disease characteristics studied included fever and rash status, previous use of DMARDs, previous use of biologics, CRP, and articular and extra-articular damage. All were similar between the placebo and ACTEMRA groups except for a higher proportion of patients with rash in the placebo group (48.6%) compared with the ACTEMRA group (29.3%). In addition, baseline CRP was lower in the placebo group in comparison with the ACTEMRA group.

The primary endpoint was the proportion of patients with at least 30% improvement in JIA ACR core set (JIA ACR30 response) at Week 12 and absence of fever (no temperature recording  $\geq 37.5^{\circ}\text{C}$  in the preceding 7 days). Eighty five percent (64/75) of the patients treated with ACTEMRA and 24.3% (9/37) of placebo patients achieved this endpoint. These proportions were highly significantly different ( $p < 0.0001$ ).

The percent of patients achieving JIA ACR 30, 50, 70 and 90 responses are shown in the table below.

**Table 9 JIA ACR response rates at week 12 (percent of patients)**

| <b>Response Rate</b> | <b>ACTEMRA<br/>n=75</b> | <b>Placebo<br/>n=37</b> |
|----------------------|-------------------------|-------------------------|
| ACR 30               | 90.7%*                  | 24.3%                   |
| ACR 50               | 85.3%*                  | 10.8%                   |
| ACR 70               | 70.7%*                  | 8.1%                    |
| ACR 90               | 37.3%*                  | 5.4%                    |

\*  $p < 0.0001$ , ACTEMRA vs. placebo



Secondary endpoints of the study included the proportion of patients with fever due to sJIA at baseline who were free of fever at week 12, corticosteroid tapering, quality of life improvements as measured by CHAQ-DI and changes in laboratory parameters.

### ***Systemic Features***

In those patients treated with ACTEMRA, 85% who had fever due to sJIA at baseline were free of fever (no temperature recording  $\geq 37.5^{\circ}\text{C}$  in the preceding 14 days) at week 12 versus only 21% of placebo patients ( $p < 0.0001$ ), and 64% of ACTEMRA-treated patients with rash characteristic of sJIA at baseline were free of rash at week 12 versus 11% of placebo patients ( $p = 0.0008$ ).

There was a highly statistically significant reduction in pain for ACTEMRA-treated patients at week 12 in comparison to placebo patients. The adjusted mean change in the pain VAS after 12 weeks of ACTEMRA treatment was a reduction of 41 points on a scale of 0 -100 compared to a reduction of 1 for placebo patients ( $p < 0.0001$ ).

### ***Corticosteroid Tapering***

Of the 31 placebo and 70 ACTEMRA patients receiving oral corticosteroids at baseline, 8 placebo and 48 ACTEMRA patients achieved a JIA ACR70 response at week 6 or 8 enabling corticosteroid dose reduction. Seventeen (24%) ACTEMRA patients versus 1 (3%) placebo patient were able to reduce the dose of corticosteroid by at least 20% without experiencing a subsequent JIA ACR30 flare or occurrence of systemic symptoms to week 12 ( $p = 0.028$ ).

### ***Quality of Life***

At week 12, the proportion of ACTEMRA-treated patients showing a minimally clinically important improvement in CHAQ-DI (defined as an individual total score decrease of  $\geq 0.13$ ) was significantly higher than in patients receiving placebo, 77% versus 19% ( $p < 0.0001$ ).

### ***Laboratory Parameters***

Fifty out of 75 (67%) patients treated with ACTEMRA had a haemoglobin  $<$  LLN at baseline. Forty (80%) of these patients with decreased haemoglobin had an increase in their haemoglobin to within the normal range at week 12, in comparison to only 2 out of 29 (7%) of placebo patients with haemoglobin  $<$  LLN at baseline ( $p < 0.0001$ ). Forty-four (88%) ACTEMRA patients with decreased haemoglobin at baseline had an increase in their haemoglobin by  $\geq 10$  g/L at week 6 versus 1 (3%) placebo patient ( $p < 0.0001$ ).

The proportion of ACTEMRA-treated patients with thrombocytosis at baseline who had a normal platelet count at week 12 was significantly higher than in the placebo patients, 90% versus 4%, ( $p < 0.0001$ ).

A marked decrease in mean levels of acute phase reactants, CRP, ESR, and serum amyloid A occurred rapidly after ACTEMRA administration.

## INDICATIONS

### **Rheumatoid Arthritis (IV and SC formulations)**

ACTEMRA is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients in combination with methotrexate (MTX) or other non-biological disease-modifying anti-rheumatic drugs (DMARDs) in case of either an inadequate response or intolerance to previous therapy with one or more DMARDs.

ACTEMRA is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients with poor prognostic factors (see *CLINICAL TRIALS*) in combination with MTX in those not previously treated with MTX.

In the two groups of patients above, ACTEMRA can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

ACTEMRA has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given in combination with methotrexate.

### **Polyarticular Juvenile Idiopathic Arthritis (IV formulation only)**

ACTEMRA is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response to or intolerance to methotrexate (MTX). ACTEMRA can be given alone or in combination with MTX.

### **Systemic Juvenile Idiopathic Arthritis (IV formulation only)**

ACTEMRA is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older. ACTEMRA can be given alone or in combination with methotrexate (MTX).

## CONTRAINDICATIONS

ACTEMRA is contraindicated in patients with:

- known hypersensitivity to any component of the product or with a history of any reaction consistent with hypersensitivity to any component of the product, Chinese hamster ovary cell products or other recombinant human or humanised antibodies
- active, severe infections (See PRECAUTIONS)

## PRECAUTIONS

In order to improve the traceability of biological medicinal products, the tradename of the administered product should be clearly recorded in the patient medical record.

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

## **All Indications**

### ***Infections***

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including ACTEMRA (see ADVERSE EFFECTS). ACTEMRA treatment should not be initiated in patients with active infections (see CONTRAINDICATIONS). If a patient develops a serious infection, administration of ACTEMRA should be interrupted until the infection is controlled. Physicians should exercise caution when considering the use of ACTEMRA in patients with a history of recurring or chronic 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 biologic treatments for moderate to severe RA, pJIA or sJIA as signs and symptoms of acute inflammation may be lessened, associated with suppression of the acute phase reaction. The effects of ACTEMRA on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients and parents/guardians of minors with pJIA or sJIA should be instructed to contact a physician immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

The use of ACTEMRA is not recommended in patients with HIV, positive core antibody for hepatitis B, prior HCV infection, or symptomatic EBV infection. Viral reactivation (e.g. hepatitis B) has been reported with biologic therapies for RA. In clinical studies with ACTEMRA, patients who screened positive for hepatitis were excluded.

In the RA long term exposure population, the overall rate of serious infections (bacterial, viral and fungal) was 4.7 events per 100 patient years. Reported serious infections, some with fatal outcome, included active tuberculosis, which may present with intrapulmonary or extrapulmonary disease, invasive pulmonary infections, including candidiasis, aspergillosis, coccidioidomycosis and pneumocystis jirovecii, pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported.

### ***Gastrointestinal Perforation - Complications of Diverticulitis***

Events of diverticular perforation as complications of diverticulitis have been reported in RA patients. ACTEMRA should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, should be evaluated promptly for early identification of gastrointestinal perforation.

### ***Tuberculosis***

As recommended for other biological treatments for RA, pJIA or sJIA, patients should be screened for latent tuberculosis (TB) infection prior to starting ACTEMRA therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating ACTEMRA. Physicians are reminded of the risk of false negative tuberculin

skin and interferon-gamma TB blood test results, especially in patients who are severely ill or immunocompromised.

Patients should be instructed to seek medical advice if signs or symptoms suggestive of a TB infection (e.g. persistent cough, wasting/weight loss, low grade fever) occur during or after therapy with ACTEMRA.

### ***Vaccinations***

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

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

In a small, randomised open-label study, adult RA patients treated with ACTEMRA plus MTX had a response to both the 23-valent pneumococcal polysaccharide (PPV) and tetanus toxoid (TTV) vaccines comparable to the response seen in patients receiving MTX only (60% vs 71% for PPV; 42% vs 39% for TTV, respectively). Because of the small number of patients in the study no firm conclusions can be drawn about the absolute differences in antibody responses between the two groups.

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

### ***Hypersensitivity Reactions, including Anaphylaxis***

Serious hypersensitivity reactions, including anaphylaxis, have been reported in association with ACTEMRA (see ADVERSE EFFECTS) and anaphylactic events with a fatal outcome have been reported with intravenous infusions of ACTEMRA. In the post-marketing setting, events of serious hypersensitivity and anaphylaxis, have occurred in patients treated with a range of doses of ACTEMRA, including intravenous and subcutaneous administration of ACTEMRA, with or without concomitant arthritis therapies, premedication and/or a previous hypersensitivity reaction.

In the post marketing setting, cases with a fatal outcome have been reported with intravenous ACTEMRA. These events have occurred as early as the first infusion of ACTEMRA (see CONTRAINDICATIONS and POST-MARKETING EXPERIENCE). Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during infusion with ACTEMRA.

The treating healthcare professional should consider the risks of potential hypersensitivity reactions when assessing a patient's suitability for home use with subcutaneous ACTEMRA. Healthcare professionals should ensure training in the subcutaneous injection technique is provided to patients. Serious hypersensitivity reactions have

occurred with subcutaneous ACTEMRA and anaphylaxis has occurred in the post-marketing setting. Hypersensitivity reactions, including anaphylaxis, may occur even after multiple injections of subcutaneous ACTEMRA. Inform patients that some patients who have been treated with ACTEMRA have developed serious allergic reactions, including anaphylaxis. Instruct patients 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 ADMINISTRATION).

If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of ACTEMRA should be stopped immediately and ACTEMRA should be permanently discontinued.

Patients with a history of any reaction consistent with hypersensitivity (e.g. urticaria, bronchospasm, angioedema) to ACTEMRA or any component of the product must not be re-challenged with ACTEMRA (see CONTRAINDICATIONS).

### ***Viral Reactivation***

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

### ***Active Hepatic Disease and Hepatic Impairment***

Treatment with ACTEMRA particularly when administered concomitantly with MTX, 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 ADVERSE EFFECTS – Laboratory Abnormalities and DOSAGE AND ADMINISTRATION – Special Patient Groups).

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

### ***Hepatic Transaminase and Laboratory Effects***

In clinical trials, transient or intermittent mild and moderate elevations of hepatic transaminases and bilirubin have been reported with ACTEMRA treatment, without progression to hepatic injury (see ADVERSE EFFECTS). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with ACTEMRA. There is a potential risk of hepatotoxicity with use of ACTEMRA.

Particular caution should be exercised when considering initiation of ACTEMRA treatment in patients with elevated ALT or AST  $> 1.5 \times$  ULN. In patients with baseline ALT or AST  $> 5 \times$  ULN, treatment with ACTEMRA is not recommended.

In RA, ALT and AST levels should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. For recommended modifications based on transaminases see DOSAGE AND ADMINISTRATION. For ALT or AST elevations  $> 3$  to  $5 \times$  ULN, confirmed by repeat testing, ACTEMRA treatment should be interrupted. Once the patient's hepatic transaminases are below  $3 \times$  ULN, treatment with ACTEMRA may recommence at 4 or 8 mg/kg for the IV formulation or every other week or weekly injection for the SC formulation.

In pJIA and sJIA, ALT and AST should be monitored at the time of the second infusion and thereafter every 4 to 8 weeks for pJIA and every 2 to 4 weeks for sJIA (see DOSAGE AND ADMINISTRATION).

### ***Haematological Abnormalities***

Decreases in neutrophil and platelet counts have occurred following treatment with ACTEMRA 8 mg/kg in combination with MTX (see section ADVERSE EFFECTS – Laboratory Abnormalities). There may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist.

In patients not previously treated with ACTEMRA, initiation is not recommended in patients with an absolute neutrophil count (ANC) below  $2 \times 10^9/L$ . Caution should be exercised when considering initiation of ACTEMRA treatment in patients with a low platelet count (i.e. platelet count  $< 100 \times 10^9/L$ ). In patients with an ANC  $< 0.5 \times 10^9/L$  or a platelet count  $< 50 \times 10^9/L$  treatment is not recommended (See PRECAUTIONS – Effects of Laboratory Tests).

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

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

In pJIA and sJIA, neutrophils and platelets should be monitored at the time of the second infusion and thereafter every 4 to 8 weeks for pJIA and every 2 to 4 weeks for sJIA (see DOSAGE AND ADMINISTRATION).

### ***Lipid Parameters***

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

Assessment of lipid parameters should be performed in RA, pJIA and sJIA 4 to 8 weeks following initiation of ACTEMRA therapy. RA and sJIA patients should then be managed according to local clinical guidelines for management of hyperlipidaemia. For

pJIA patients assessment of lipid parameters should be performed at 3 monthly intervals during ACTEMRA treatment until it is clear the risk of development of significant changes in lipid parameters has diminished.

### ***Demyelinating Disorders***

Physicians should be vigilant for symptoms potentially indicative of new-onset central demyelinating disorders. The potential for central demyelination with ACTEMRA is currently unknown. Multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in RA clinical studies.

### ***Malignancy***

The risk of malignancy is increased in patients with RA. Immunomodulatory medicinal products may increase the risk of malignancy.

### ***Intravenous Infusion Reactions***

Infusion reactions have been observed during and within 24 hours of treatment with ACTEMRA (see ADVERSE EFFECTS – Infusion Reactions).

### ***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 (see PRECAUTIONS – Lipid Parameters). Elevations in LDL and HDL lipids have been observed, with no clinical consequences identified. No data are available concerning cardiovascular outcomes with long-term use of ACTEMRA.

### ***Combination with TNF Antagonists and/or other Biological Therapies***

There is no experience with the use of ACTEMRA with TNF antagonists or other biological treatments for RA. ACTEMRA is not recommended for use with other biological agents including TNF antagonists, anakinra, rituximab and abatacept.

### ***Sodium***

Intravenous ACTEMRA contains 1.17 mmol (26.55 mg) of sodium per maximum dose of 1200 mg. This should be taken into consideration by patients on a controlled sodium diet. Doses below 1025 mg of ACTEMRA contain less than 1 mmol of sodium (23 mg) and can essentially be considered ‘sodium free’.

The subcutaneous ACTEMRA formulation does not contain sodium.

### ***Effects on Fertility***

Preclinical data do not suggest an effect on fertility under treatment with a murine 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 reproductive performance affected in IL-6 deficient male and female mice.

### ***Use in Pregnancy - Category C***

ACTEMRA should not be used during pregnancy unless clearly necessary. There are no adequate data from the use of ACTEMRA in pregnant women. The potential risk for humans is unknown. Women of childbearing potential should be advised to use adequate contraception during and for several months after therapy with ACTEMRA.

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 in the 10 mg/kg/day mid-dose group (> 35 times human exposure) and in the 50 mg/kg/day high-dose group (> 100 times human exposure) compared to vehicle control and low-dose groups. It cannot be excluded that this finding is related to ACTEMRA treatment. Placental transfer of both tocilizumab and anti-tocilizumab antibodies to the foetus was seen in cynomolgus monkeys.

### ***Use in Lactation***

It is unknown whether tocilizumab is excreted in human breast milk and its efficacy and safety in lactating women has not been established. However, it is known that endogenous immunoglobulins of the IgG isotype are excreted into human milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with ACTEMRA should be made taking into account the benefit of breast-feeding to the child and the benefit of ACTEMRA therapy to the woman.

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

### ***Paediatric Use***

The safety and efficacy of intravenous ACTEMRA in children below 18 years of age with conditions other than pJIA and sJIA have not been established. Ten patients who participated in the pivotal study for pJIA were less than 4 years of age. Children under the age of two have not been studied.

Available data only support use of intravenous ACTEMRA in children with pJIA who have had an inadequate response to or intolerance to MTX. Long-term safety data for intravenous ACTEMRA use in children with pJIA are currently limited to 2 years, and at present no comparison with the safety profile of other biological DMARDs approved for use in this indication has been made.

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 safety and efficacy of subcutaneous ACTEMRA in children from birth to less than 18 years have not been established. No data are available.



### ***Use in the Elderly***

Population analyses evaluated the potential effects of demographic characteristics on the pharmacokinetics of ACTEMRA in adult RA patients. Results of these analyses showed that no adjustment of the dose is necessary for age, gender, or race.

No dose adjustment is required in elderly patients.

### ***Genotoxicity***

Standard genotoxicity studies with tocilizumab in both prokaryotic and eukaryotic cells were negative.

### ***Carcinogenicity***

A carcinogenicity study of ACTEMRA has not been conducted. Proliferating lesions were not observed in a chronic cynomolgus monkey 6-month toxicity study.

### ***Effects on Laboratory Tests***

Caution should be exercised when considering initiation of ACTEMRA treatment in patients with a low neutrophil count. Decreases in neutrophil counts below  $1 \times 10^9/L$  occurred in 3.4%, with counts  $< 0.5 \times 10^9/L$  occurring in 0.3%, of patients on ACTEMRA 8 mg/kg + DMARD without clear association with serious infection (see PRECAUTIONS – Haematological Abnormalities; ADVERSE EFFECTS - Laboratory Abnormalities). In patients with an absolute neutrophil count  $< 0.5 \times 10^9/L$  treatment is not recommended.

### ***Ability to Drive and Use Machines***

No studies on the effects on the ability to drive and use machines have been performed and there is no evidence from the available data that ACTEMRA treatment affects the ability to drive and use machines. However, given that dizziness has been reported, patients who experience this adverse reaction should be advised not to drive or use machines until it has resolved.

### **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, ACTEMRA has not been studied in patients during an episode of active MAS (see ADVERSE EFFECTS).

## **INTERACTIONS WITH OTHER MEDICINES**

Population pharmacokinetic analyses did not detect any effect of MTX, non-steroidal anti-inflammatory drugs or corticosteroids on tocilizumab clearance.

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.

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

The expression of hepatic CYP450 enzymes is suppressed by cytokines that stimulate chronic inflammation, such as IL-6. Thus suppression of 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 CYP3A4 and to a lesser extent CYP1A2, CYP2C9 and CYP2C19 enzyme messenger RNA (mRNA) expression. Tocilizumab was shown to normalise expression of the mRNA for these enzymes.

This 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 and its acid metabolite (CYP3A4 substrates) were decreased by 57% and 39%, respectively, one week following a single dose of tocilizumab, to a level similar or slightly higher than those observed (in other studies) in healthy subjects.

When starting or stopping therapy with ACTEMRA, patients taking medicinal products which are individually adjusted and are metabolised via CYP450 3A4, 1A2, 2C9 or 2C19 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporin or benzodiazepines) should be monitored as doses may need to be adjusted to maintain therapeutic effect. The degree of dose up-titration upon initiation of therapy or dose down-titration when stopping therapy with ACTEMRA should be based on the therapeutic response and/or adverse effects of the patient to the individual medicine. Given a relatively long elimination half-life ( $t_{1/2}$ ), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

## **ADVERSE EFFECTS**

### **Rheumatoid Arthritis**

#### ***Patients Treated with Intravenous ACTEMRA***

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

The *all control* population includes all patients who received at least one dose of ACTEMRA in the double-blind controlled period of the 5 studies. 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 ACTEMRA 4 mg/kg in combination with MTX, 1870 patients received ACTEMRA 8 mg/kg in combination with MTX/other DMARDs and 288 patients received ACTEMRA 8 mg/kg monotherapy.

The *all 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 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. The mean duration of exposure to ACTEMRA in the *all exposure* population was 2.14 years.

The most commonly reported AEs in controlled studies up to 2 years (occurring in  $\geq 5\%$  of patients treated with ACTEMRA monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT and bronchitis. In study II the rate of AEs (including deaths, serious AEs and AEs leading to treatment withdrawal or dose modification) after 2 years, calculated as a function of exposure (i.e. events per 100 patient years), had not increased in comparison with the AE profile observed after 1 year of study II.

**Table 10 Adverse Events occurring in at least 2% or more of patients on 8 mg/kg ACTEMRA + DMARD and at least 1% greater than that observed in patients on placebo + DMARD**

| <b>All Control Study Population</b> |  |                      |                                      |   |                             |
|-------------------------------------|--|----------------------|--------------------------------------|---|-----------------------------|
|                                     | <b>ACTEMRA<br/>8 mg/kg<br/>monotherapy</b> | <b>MTX</b>           | <b>ACTEMRA<br/>4 mg/kg +<br/>MTX</b> | <b>ACTEMRA<br/>8 mg/kg +<br/>DMARDs</b> | <b>Placebo +<br/>DMARDs</b> |
| <b>Preferred Term</b>               | <b>n=288<br/>(%)</b>                       | <b>n=284<br/>(%)</b> | <b>n=774<br/>(%)</b>                 | <b>n=1870<br/>(%)</b>                   | <b>n=1555<br/>(%)</b>       |
| Upper Respiratory Tract Infection   | 7  | 5                    | 9                                    | 9                                       | 7                           |
| Nasopharyngitis                     | 7  | 6                    | 5                                    | 7                                       | 5                           |
| Headache                            | 7  | 2                    | 6                                    | 6                                       | 4                           |
| Hypertension                        | 6  | 2                    | 6                                    | 5                                       | 3                           |
| Cough                               | 3  | 0                    | 3                                    | 3                                       | 2                           |
| ALT increased                       | 6  | 4                    | 3                                    | 3                                       | 1                           |
| Diarrhoea                           | 5  | 5                    | 5                                    | 4                                       | 4                           |
| Back Pain                           | 2  | 1                    | 3                                    | 4                                       | 3                           |
| Peripheral Oedema                   | 2  | 0                    | 2                                    | 3                                       | 1                           |
| Dizziness                           | 3  | 1                    | 2                                    | 3                                       | 2                           |
| Bronchitis                          | 3  | 2                    | 4                                    | 3                                       | 3                           |
| Rash                                | 2  | 1                    | 4                                    | 3                                       | 1                           |
| Mouth Ulceration                    | 2  | 2                    | 1                                    | 2                                       | 1                           |
| Abdominal Pain Upper                | 2  | 2                    | 3                                    | 3                                       | 2                           |
| Gastritis                           | 1  | 2                    | 2                                    | 2                                       | 1                           |
| Transaminase increased              | 1  | 5                    | 3                                    | 3                                       | 1                           |

Other infrequent and medically relevant adverse events occurring at an incidence of less than 2% in RA patients treated with ACTEMRA in controlled trials were:

*Infections and infestations:* cellulitis, oral herpes simplex, herpes zoster, diverticulitis

*Gastrointestinal disorders:* stomatitis, gastric ulcer

*Skin and subcutaneous tissue disorders:* pruritus, urticaria

*Investigations:* weight increased, total bilirubin increased

*Blood and lymphatic system disorders:* leucopenia, neutropenia

*Metabolism and nutrition disorders:* hypercholesterolaemia, hypertriglyceridaemia

*General disorders and administration site conditions:* hypersensitivity reaction

*Respiratory, thoracic and mediastinal disorders:* dyspnoea

*Eye disorders:* conjunctivitis

*Renal disorders:* nephrolithiasis

*Endocrine disorders: hypothyroidism*

### Infections

In the 6 month controlled clinical trials, the rate of all infections reported with ACTEMRA 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 ACTEMRA was 108 events per 100 pt years exposure.

In the 6 month controlled clinical trials, the rate of serious infections (bacterial, viral and fungal) with ACTEMRA 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 ACTEMRA 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 active tuberculosis, which may present with intrapulmonary or extrapulmonary disease, invasive pulmonary infections, including candidiasis, aspergillosis, coccidioidomycosis and pneumocystis jirovecii, pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have also been reported.

### Gastrointestinal Perforation

During the 6 month controlled clinical trials, the overall rate of gastrointestinal (GI) perforation was 0.26 events per 100 pt years with ACTEMRA therapy. In the *all exposure* population the overall rate of gastrointestinal perforation was 0.28 events per 100 pt years. Reports of gastrointestinal perforation were primarily reported as complications of diverticulitis including generalised purulent peritonitis, lower GI perforation, fistulae 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 ACTEMRA 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 anaphylactic reactions (occurring in a total of 8/4009 patients, 0.2%) was several fold higher with the 4 mg/kg dose, compared to the 8 mg/kg dose.

Clinically significant hypersensitivity reactions associated with ACTEMRA and requiring treatment discontinuation, were reported in a total of 56 out of 4009 patients (1.4%) treated with ACTEMRA during the controlled and open label clinical trials.

These reactions were generally observed during the second to fifth infusions of ACTEMRA.

### 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 (FUNCTION) 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 ACTEMRA treatment groups was consistent with the known safety profile of ACTEMRA (Table 9).

The overall rate of serious adverse events (SAEs) per 100 patient years (PY) was numerically higher for the ACTEMRA arms (13.2 SAEs per 100 PY) than the placebo + MTX arm (10.6 SAEs per 100 PY). These were reported under 'Infections and Infestations', 'Neoplasms Benign, Malignant and Unspecified', 'Respiratory, Thoracic and Mediastinal Disorders' and 'Injury, Poisoning and Procedural Complications'.

The rate of discontinuation due to an adverse event was approximately twice as high in the ACTEMRA arms, as in the placebo + MTX arm (16.1 and 8.2 events per 100 PY respectively). In all 3 ACTEMRA treatment arms, the most common reason for treatment discontinuation was attributed to 'Investigations' events, in particular events related to liver enzyme elevations. In the study there were 14 patient deaths reported, 12 in ACTEMRA-treated patients and 2 in Placebo + MTX-treated patients.

### ACTEMRA vs adalimumab in monotherapy

In a 24 week double-blinded, parallel study (monotherapy with ACTEMRA 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 ACTEMRA and adalimumab. The proportion of patients with serious adverse events was balanced between the treatment groups (ACTEMRA 11.7% vs. adalimumab 9.9%) with the most common event being infections (3.1% each). There was a sudden death in the ACTEMRA arm of a patient who died 10 days after the last dose. The cause of death was unknown. The patient had a history of peripheral vascular disease, hypertension, smoking and interstitial lung disease. 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 ACTEMRA compared with adalimumab. Four (2.5%) patients in the ACTEMRA 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 ACTEMRA arm and 5 (3.1%) patients in the adalimumab arm experienced ALT increases of CTC grade 2 or higher. For patients not receiving lipid lowering agents the mean increase in LDL from baseline to week 24 was 0.64 mmol/L (25 mg/dL) for patients in the ACTEMRA arm and 0.19 mmol/L (7 mg/dL) for patients in the adalimumab arm. The safety observed in the ACTEMRA arm

was consistent with the known safety profile of ACTEMRA and no new or unexpected adverse drug reactions were observed.

### ***Patients Treated with Subcutaneous ACTEMRA***

The safety of subcutaneous ACTEMRA includes data from Study VI (SUMMACTA) and Study VII (BREVACTA). SUMMACTA compared the efficacy and safety of subcutaneous ACTEMRA 162 mg administered every week versus intravenous ACTEMRA 8 mg/kg every 4 weeks in 1262 subjects with adult RA. BREVACTA was a placebo-controlled superiority study that evaluated the safety and efficacy of subcutaneous ACTEMRA 162 mg administered every other week or placebo in 656 patients. All patients in both studies received background non-biological DMARD(s).

The safety and immunogenicity observed for subcutaneous ACTEMRA was consistent with the known safety profile of intravenous ACTEMRA and no new or unexpected adverse drug reactions were observed (see Table 10). A higher frequency of injection site reactions was observed in patients who received subcutaneous ACTEMRA compared with those who received subcutaneous placebo injections (in the IV arms of the studies).

### ***Injection Site Reactions***

During the 6-month controlled period in SUMMACTA, the frequency of injection site reactions was 10.1% (64/631) and 2.4% (15/631) for the subcutaneous ACTEMRA and the subcutaneous placebo (in the IV arm of the study) weekly injections, respectively. In BREVACTA, the frequency of injection site reactions was 7.1% (31/437) and 4.1% (9/218) for the subcutaneous ACTEMRA and placebo every other week, respectively. These injection site reactions (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 SUMMACTA, a total of 625 patients treated with ACTEMRA 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 neutralising anti-tocilizumab antibodies. In BREVACTA, a total of 434 patients treated with ACTEMRA 162 mg every other week were tested for anti-tocilizumab antibodies. Seven patients (1.6%) in the subcutaneous ACTEMRA arm developed anti-tocilizumab antibodies; of these 6 (1.4%) in the subcutaneous ACTEMRA arm developed neutralising antibodies.

A total of 1454 subcutaneous ACTEMRA all exposure patients have been tested for anti-tocilizumab antibodies, 13 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.

### *Hypersensitivity and Anaphylaxis*

In the subcutaneous ACTEMRA development program clinically significant hypersensitivity reactions were defined as any adverse event during or within 24 hours of an injection (excluding injection site reactions), related to treatment and leading to study withdrawal. Clinically significant hypersensitivity reactions were experienced in 0.7% (8 out of 1068) of patients in the subcutaneous 6-month controlled RA trials and 0.7% (10 out of 1465) of patients in the subcutaneous all-exposure population. The events included, but were not limited to hypersensitivity (5 events) and urticaria (1 event).

There were no cases of anaphylaxis in the subcutaneous ACTEMRA pivotal studies SUMMACTA and BREVACTA, however anaphylaxis has been reported in the post-market setting.

### *Polyarticular Juvenile Idiopathic Arthritis*

The safety of intravenous ACTEMRA was studied in 188 paediatric patients, 2 to 17 years of age, with pJIA who had an inadequate clinical response or were intolerant to MTX. The total patient exposure in the ACTEMRA all exposure population was 184.4 pt years. In general, with the exception of MAS, the types of adverse drug reactions (ADRs) in patients with pJIA were similar to those seen in RA and sJIA patients.

The overall safety profile remained unchanged through Week 104 of the study, and was consistent with the safety experience at Week 40. The majority of AEs reported were mild or moderate in intensity, reversible and not treatment-limiting.

### ***Infections***

The rate of infections in the ACTEMRA all exposure population was 163.7 per 100 pt years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was 4.9 per 100 pt years. The rate of serious infections was numerically higher in patients weighing < 30 kg treated with 10 mg/kg ACTEMRA (12.2 per 100 pt years) compared to patients weighing ≥ 30 kg, treated with 8 mg/kg ACTEMRA (4.0 per 100 pt years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing < 30 kg treated with 10 mg/kg ACTEMRA (21%) compared to patients weighing ≥ 30 kg, treated with 8 mg/kg ACTEMRA (8%).

### ***Infusion Reactions***

In pJIA patients, infusion related reactions are defined as all events occurring during or within 24 hours of an infusion. In the ACTEMRA all exposure population, 11 patients (5.9%) experienced infusion reactions during the infusion, and 38 patients (20.2%) experienced an event within 24 hours of an infusion. The most common events occurring during infusion were headache, nausea and hypotension and within 24 hours of infusion were dizziness and hypotension. In general, the ADRs observed during or within 24 hours of an infusion were similar in nature to those seen in RA and sJIA patients.

No clinically significant hypersensitivity reactions were reported.

### ***Immunogenicity***

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

### **Systemic Juvenile Idiopathic Arthritis**

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

In general, the ADRs in patients with sJIA were similar in type to those seen in RA and pJIA patients (see ADVERSE EFFECTS – Rheumatoid Arthritis).

### ***Infections***

In the 12 week controlled trial the rate of all infections in the ACTEMRA group was 344.7 per 100 patient years and 287.0 per 100 patient years in the placebo group. In the on-going open label extension study (Part II) the overall rate of infections remained similar at 306.6 per 100 patient years.

In the 12 week controlled trial the rate of serious infections in the ACTEMRA group was 11.5 per 100 patient years. In the on-going open label extension study the overall rate of serious 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.

In Australia, a case of fatal sepsis occurred in a 6-year old who had been treated with ACTEMRA for approximately 2 years for sJIA. Methotrexate was given concomitantly. The patient had symptoms of gastroenteritis on the day preceding his death, and the last dose of ACTEMRA was administered 10 days prior to the event. The death was assessed as related to septicemia.

### ***Macrophage Activation Syndrome***

In the 12 week controlled study, no patient in any treatment group experienced macrophage activation syndrome (MAS) while on assigned treatment. Three per 112 (3%) developed MAS during open-label treatment with ACTEMRA. One patient in the placebo group escaped to ACTEMRA 12 mg per kg at Week 2 due to severe disease activity, and ultimately developed MAS at Day 70. Two additional patients developed MAS during the long-term extension. All 3 patients had ACTEMRA dose interrupted (2 patients) or discontinued (1 patient) for the MAS event, received treatment, and the MAS resolved without sequelae. Based on a limited number of cases, the incidence of MAS does not appear to be elevated in the ACTEMRA sJIA clinical development experience, however no definitive conclusions can be made.



A case of MAS with a fatal outcome was reported in a patient enrolled in a clinical study of ACTEMRA in sJIA. The patient had interrupted ACTEMRA treatment 4 weeks prior to the onset of MAS because of a rotavirus infection. The patient also experienced a worsening of sJIA prior to the diagnosis of MAS.

### ***Infusion Reactions***

For sJIA patients, infusion related reactions are defined as all events occurring during or within 24 hours of an infusion. In the 12 week controlled trial, 4.0% of patients from the ACTEMRA group experienced events occurring during infusion, one event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment.

In the 12 week controlled trial experience, 16% of patients in the ACTEMRA group and 5.4% of patients in the placebo group experienced an event within 24 hours of infusion. In the ACTEMRA group, the events included, but not limited to rash, urticaria, diarrhoea, epigastric discomfort, arthralgia and headache. One of these events (urticaria) was considered serious.

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

Reports of anaphylaxis, anaphylactoid reactions, and hypersensitivity reactions in patients under 18 years of age have been reported in the post-marketing setting.

### ***Immunogenicity***

All 112 patients were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti-tocilizumab antibodies with one of these patients having a hypersensitivity reaction leading to withdrawal.

### **Laboratory Abnormalities**

#### ***Haematology abnormalities***

##### **Rheumatoid Arthritis**

##### ***Neutrophils – Intravenous Administration***

In the 6 month controlled trials decreases in neutrophil counts below  $1 \times 10^9/L$  occurred in 3.4% of patients on ACTEMRA 8 mg/kg + DMARD compared to < 0.1% of patients on placebo + DMARD. Approximately half of the patients who developed an ANC <  $1 \times 10^9/L$  did so within 8 weeks after starting therapy. Decreases below  $0.5 \times 10^9/L$  were reported in 0.3% patients receiving ACTEMRA 8 mg/kg + DMARD (see PRECAUTIONS – Effects on Laboratory Tests).

There was no clear relationship between decreases in neutrophils below  $1 \times 10^9/L$  and the occurrence of serious infections.

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.

#### *Neutrophils - Subcutaneous Administration*

During routine laboratory monitoring in the ACTEMRA 6-month controlled period of SUMMACTA and BREVACTA, a decrease in neutrophil count below  $1 \times 10^9/L$  occurred in 2.9% and 2.3% of patients on ACTEMRA 162 mg SC weekly and every other week, respectively.

There was no clear relationship between decreases in neutrophils below  $1 \times 10^9/L$  and the occurrence of serious infections.

#### *Platelets – Intravenous Administration*

In the 6 month controlled trials, decreases in platelet counts below  $100 \times 10^9/L$  occurred in 1.7% of patients on ACTEMRA 8 mg/kg + DMARDs compared to < 1% on placebo + DMARDs. These decreases occurred without associated bleeding events. (See DOSAGE AND ADMINISTRATION and PRECAUTIONS – Haematological Abnormalities.)

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.

#### *Platelets - Subcutaneous Administration*

During routine laboratory monitoring in the 6-month controlled period of SUMMACTA and BREVACTA, 1.6% and 1.4% of patients experienced a decrease in platelet count to  $< 100 \times 10^9/L$  on ACTEMRA 162 mg SC weekly and every other week, respectively.

#### *Polyarticular Juvenile Idiopathic Arthritis*

##### *Neutrophils*

During routine laboratory monitoring in the ACTEMRA all exposure population, a decrease in neutrophil count below  $1 \times 10^9/L$  occurred in 3.7% of patients. There was no clear relationship between decreases in neutrophils below  $1 \times 10^9/L$  and the occurrence of serious infections.

##### *Platelets*

During routine laboratory monitoring in the ACTEMRA all exposure population, 1% of patients had a decrease in platelet count to  $\leq 50 \times 10^3/\mu L$  without associated bleeding events.

#### *Systemic Juvenile Idiopathic Arthritis*

##### *Neutrophils*

During routine laboratory monitoring in the 12 week controlled trial, a decrease in neutrophil counts below  $1 \times 10^9/L$  occurred in 7% of patients in the ACTEMRA group, and in none in the placebo group. In the ongoing open-label extension study decreases in neutrophil counts below  $1 \times 10^9/L$  occurred in 15% of patients in the ACTEMRA group.

There was no clear relationship between decreases in neutrophils below  $1 \times 10^9/L$  and the occurrence of serious infections.

### *Platelets*

During routine laboratory monitoring in the 12 week controlled trial, 3% of patients in the placebo group and 1% in the ACTEMRA group had a decrease in platelet count to  $\leq 100 \times 10^3/\mu\text{L}$ . In the ongoing open-label extension study decreases in platelet counts below  $100 \times 10^3/\mu\text{L}$  occurred in 3% of patients in the ACTEMRA group, without associated bleeding events.

### ***Liver enzyme elevations***

#### *Rheumatoid Arthritis*

##### *Intravenous Administration*

During the 6 month controlled trials transient elevations in ALT (alanine transaminase)/AST (aspartate transaminase)  $> 3 \times \text{ULN}$  (Upper Limit of Normal) were observed in 2.1% of patients on ACTEMRA 8 mg/kg compared to 4.9% of patients on MTX, and in 6.5% of patients who received ACTEMRA 8 mg/kg + DMARD compared to 1.5% of patients on placebo + DMARD. The addition of potentially hepatotoxic drugs (for example MTX) to ACTEMRA monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST  $> 5 \times \text{ULN}$  were observed in 0.7% of ACTEMRA monotherapy patients and 1.4% of ACTEMRA + DMARD patients, the majority of whom were discontinued from ACTEMRA treatment. These elevations were not associated with any clinically relevant increases in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic insufficiency. During routine laboratory monitoring, the incidence of indirect bilirubin  $> \text{ULN}$  is 6.2% in patients treated with 8 mg/kg ACTEMRA + 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 VIII (FUNCTION), MTX-naïve adult patients with moderate to severe, active early RA (mean disease duration  $\leq 6$  months) experienced more transient elevations in ALT  $> 3 \times \text{ULN}$  compared with the *all control* population. Transient elevations in ALT  $> 3$  to  $5 \times \text{ULN}$  were observed in 6.6% of patients on ACTEMRA 4 mg/kg + MTX, 9.7% of patients on ACTEMRA 8mg/kg + MTX compared to 3.4% of patients on ACTEMRA 8 mg/kg + placebo and 3.9% of patients on MTX + placebo.

##### *Subcutaneous Administration*

During routine laboratory monitoring in the ACTEMRA 6-month controlled period of SUMMACTA, elevation in ALT or AST  $\geq 3 \times \text{ULN}$  occurred in 6.5% and 1.4% of patients, respectively on the SC weekly dose. In the 6-month controlled period of BREVACTA, elevation in ALT or AST  $\geq 3 \times \text{ULN}$  occurred in 3.4% and 0.7% of patients, respectively on the SC every other week dose.

#### *Polyarticular Juvenile Idiopathic Arthritis*

During routine laboratory monitoring in the ACTEMRA all exposure population, elevation in ALT or AST  $\geq 3 \times \text{ULN}$  occurred in 3.7% and  $< 1\%$  of patients, respectively.

### Systemic Juvenile Idiopathic Arthritis

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

In the ongoing open-label extension study, elevation in ALT or AST  $\geq 3$  x ULN occurred in 12% and 4% of patients, respectively, in the ACTEMRA group.

### ***Elevations in lipid parameters***

#### Rheumatoid Arthritis

##### *Intravenous Administration*

During routine laboratory monitoring in the 6 month controlled clinical trials, increases of lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol have been reported commonly. Approximately 24% of patients receiving ACTEMRA in clinical trials experienced sustained elevations in total cholesterol  $> 6.2$  mmol/L (240 mg/dL), with 15% experiencing a sustained increase in LDL to  $\geq 4.1$  mmol/L (160 mg/dL). Elevations in lipid parameters 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 6-month controlled periods of SUMMACTA and BREVACTA, 19% of patients on the SC weekly dose and 20% of patients dosed every other week experienced sustained elevations in total cholesterol  $> 6.2$  mmol/L (240 mg/dL), with 9% and 10% experiencing a sustained increase in LDL to  $\geq 4.1$  mmol/L (160 mg/dL) on the SC weekly dose and every other week dose.

#### Polyarticular Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the ACTEMRA all exposure population, the highest post-baseline values for total cholesterol were  $> 1.5$ - $2$  x ULN in one patient (0.5%) and for LDL  $> 1.5$ - $2$  x ULN in one patient (0.5%). Of 185 patients assessed 19 patients experienced consecutive sustained elevation of their total cholesterol value  $\geq 4.4$  mmol/L (170 mg/dL) at any time during study treatment.

### Systemic Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the 12 week controlled trial, elevation in total cholesterol  $>1.5$  x ULN to 2 x ULN occurred in 1.5% of the ACTEMRA group and in 0% of placebo patients. Elevation in LDL  $>1.5$  x ULN to 2 x ULN occurred in 1.9% of patients in the ACTEMRA group and 0% of the placebo group.

In the ongoing open-label extension study the pattern and incidence of elevations in lipid parameters remained consistent with the 12 week controlled trial data. Of 107 patients

assessed 22 experienced consecutive sustained elevation of their total cholesterol value  $\geq$  4.4 mmol/L (170 mg/dL) at any time during study treatment.

### **Malignancies**

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

### **Post-Marketing Experience**

The safety profile in post-marketing experience is consistent with clinical trial data with the exception of:

*Immune system disorders:* reports of fatal anaphylaxis during intravenous ACTEMRA treatment (see CONTRAINDICATIONS and PRECAUTIONS – Hypersensitivity Reactions).

*Skin and subcutaneous tissue disorders:* Stevens-Johnson Syndrome (SJS) has been reported during treatment with ACTEMRA.

*Respiratory, thoracic and mediastinal disorders:* There have been reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

*Blood and lymphatic system disorders:* very rare reports of pancytopenia have occurred.

## **DOSAGE AND ADMINISTRATION**

Treatment should be initiated by healthcare professionals experienced not only in the diagnosis and treatment of RA, pJIA or sJIA but also in the use of biological therapies for these conditions. For pJIA and sJIA treatment should be prescribed by medical practitioners experienced in the management of these conditions.

For adult patients with RA, ACTEMRA may be administered as an IV infusion or an SC injection.

For patients with pJIA and sJIA, ACTEMRA is administered as an IV infusion. For the treatment of pJIA and sJIA ACTEMRA should be administered in a hospital setting with immediate access to the necessary medical personnel and full resuscitation facilities (see PRECAUTIONS - Hypersensitivity Reactions, ADVERSE EFFECTS - Infusion Reactions and Post-marketing Experience). Subcutaneous ACTEMRA is only indicated in the treatment of patients with adult RA and is not indicated for the treatment of patients with pJIA or sJIA.

### **Rheumatoid Arthritis in Adults (IV or SC formulation)**

#### ***Intravenous Dosing Regimen***

The recommended dose of ACTEMRA for adult patients is 8 mg/kg given once every 4 weeks as an IV infusion.

For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended (see PHARMACOLOGY – PHARMACOKINETICS).

ACTEMRA can be used alone or in combination with MTX and/or other non-biological DMARDs.

ACTEMRA IV formulation is not intended for SC administration.

ACTEMRA IV formulation should be diluted by a healthcare professional with sterile 0.9% w/v sodium chloride solution using aseptic technique (see section Preparation and Administration Instructions).

It is recommended that an IV infusion of ACTEMRA is given over 1 hour.

During IV infusion, and for 30 minutes post-infusion with ACTEMRA, the patient must be closely monitored at all times for any signs or symptoms of a hypersensitivity reaction. Should any such reaction occur then appropriate urgent responses and treatments are to be initiated. The necessary equipment, treatments and protocols sufficient to initiate the management of acute anaphylaxis are to be in place along with the availability of appropriately trained personnel. There must be continued education and training of the health care professionals who administer the infusions. As part of the informed consent process patients should be made aware of the risk of anaphylaxis and the equipment, treatments and protocols in place to manage this risk.

### ***Subcutaneous Dosing Regimen***

The recommended dose of ACTEMRA for adult patients is 162 mg given once every week as a subcutaneous injection.

ACTEMRA can be used alone or in combination with MTX and/or other non-biological DMARDs.

ACTEMRA SC formulation is not intended for IV administration.

### ***Method of administration***

Subcutaneous ACTEMRA formulation is administered with a single-use pre-filled syringe.

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. Administration in the thigh may result in slightly increased absorption compared to the other recommended injection sites but this is not considered clinically relevant.

At least the first injection must be performed under the supervision of a qualified healthcare professional, in a healthcare facility with the necessary medical treatment available (including resuscitation equipment, protocols and appropriately trained personnel) in case of the need to initiate management of serious hypersensitivity reactions, including anaphylaxis. The patient must be closely monitored during the injection and afterwards for any signs and symptoms of a hypersensitivity reaction. Patients transitioning from IV ACTEMRA 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.

Subcutaneous ACTEMRA is intended for use under the guidance and supervision of the patient's treating physician. After proper training in injection technique, patients may self-inject with ACTEMRA only if their treating physician determines that it is appropriate and is satisfied that the patient can safely self-inject in the home environment and with medical follow-up as necessary.

Assess suitability of patient for SC home use and instruct patients 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 PRECAUTIONS, Hypersensitivity Reactions). Treating healthcare professionals must ensure that the patient is aware of the signs of hypersensitivity and the risk of anaphylaxis, and is capable of seeking assistance should early features of a serious hypersensitivity reaction occur.

#### Missed Dose

If a patient misses a weekly injection of ACTEMRA within 7 days of the scheduled dose, they should be instructed to take the missed dose on the next scheduled day. If a patient misses a fortnightly (i.e. every other week) injection of ACTEMRA within 7 days of the scheduled dose, they should be instructed to take the missed dose immediately and the next dose on the next scheduled day.

#### ***Dose Modification Recommendations for RA***

- Liver enzyme abnormalities

| <b>Lab Value</b> | <b>Action</b>  |
|------------------|--|
| > 1 to 3 x ULN   | <p>Dose modify concomitant DMARDs if appropriate</p> <p>For patients receiving intravenous ACTEMRA with persistent increases in this range, reduce ACTEMRA dose to 4 mg/kg or interrupt ACTEMRA until ALT/AST have normalised.</p> <p>Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate.</p> <p>For patients receiving subcutaneous ACTEMRA with persistent increases in this range, reduce ACTEMRA</p> |

|                |   |
|----------------|---|
|                | injection frequency to every other week or interrupt ACTEMRA until ALT/AST have normalised. Restart with weekly injection or injection every other week, as clinically appropriate.   |
| > 3 to 5 x ULN | Interrupt ACTEMRA dosing until < 3 x ULN and follow recommendations above for > 1 to 3 x ULN<br><br>For persistent increases > 3 x ULN (confirmed by repeat testing, see PRECAUTIONS - Hepatic Transaminase and Laboratory Effects), discontinue ACTEMRA. |
| > 5 x ULN      | Discontinue ACTEMRA.  |

- Low absolute neutrophil count (ANC)

| Lab Value<br>(cells x 10 <sup>9</sup> /L) | Action   |
|---|--|
| ANC > 1                                   | Maintain dose.   |
| ANC 0.5 to 1                              | Interrupt ACTEMRA dosing.<br><br>For patients receiving intravenous ACTEMRA, when ANC > 1 x 10 <sup>9</sup> /L resume ACTEMRA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate.<br><br>For patients receiving subcutaneous ACTEMRA, when ANC > 1 x 10 <sup>9</sup> /L resume ACTEMRA injection every other week and increase frequency to every week, as clinically appropriate. |
| ANC < 0.5                                 | Discontinue ACTEMRA.   |

- Low platelet count

| Lab Value<br>(cells x 10 <sup>9</sup> /L) | Action  |
|---|---|
| 50 to 100                                 | Interrupt ACTEMRA dosing<br><br>For patients receiving intravenous ACTEMRA, when platelet count is > 100 x 10 <sup>9</sup> /L resume ACTEMRA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate.<br><br>For patients receiving subcutaneous ACTEMRA, when platelet count is > 100 x 10 <sup>9</sup> /L resume ACTEMRA injection every other week and increase frequency to every week, as clinically appropriate. |
| < 50                                      | Discontinue ACTEMRA.  |



**Polyarticular Juvenile Idiopathic Arthritis (pJIA) (IV formulation only)**

The recommended dose of ACTEMRA for patients with pJIA is:

- 10 mg/kg for patients < 30 kilograms,
- 8 mg/kg for patients  $\geq$  30 kilograms,

given once every four weeks as an IV infusion. A change in dose should only be based on a consistent change in the patient's body weight over time. ACTEMRA can be used alone or in combination with MTX.

It is recommended that an IV infusion of ACTEMRA is given over 1 hour.

**Systemic Juvenile Idiopathic Arthritis (sJIA) (IV formulation only)**

The recommended dose of ACTEMRA for patients with sJIA is:

- 12 mg/kg for patients < 30 kilograms,
- 8 mg/kg for patients  $\geq$  30 kilograms,

given once every two weeks as an IV infusion. A change in dose should only be based on a consistent change in the patient's body weight over time. ACTEMRA can be used alone or in combination with MTX.

It is recommended that an IV infusion of ACTEMRA is given over 1 hour.

***Dose Modification Recommendations for pJIA and sJIA:***

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

**Special Patient Groups**

**Children:** The safety and efficacy of ACTEMRA in children below 18 years of age with conditions other than pJIA or sJIA have not been established. Children under the age of two have not been studied.

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

**Renal impairment:** No dose adjustment is required in patients with mild renal impairment (see PHARMACOLOGY – Pharmacokinetics in Special Populations). ACTEMRA has not been studied in patients with moderate to severe renal impairment.

***Hepatic impairment:*** The safety and efficacy of ACTEMRA has not been studied in patients with hepatic impairment (see PRECAUTIONS – Active Hepatic Disease and Hepatic Impairment) and therefore no dose recommendations can be made.

### **Preparation and Administration Instructions**

#### ***Concentrated solution for intravenous infusion***

Parenteral medications should be inspected visually for particulate matter or discolouration prior to administration.

Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles must be infused.

#### ***Rheumatoid Arthritis***

From a 100 mL infusion bag, withdraw a volume of 0.9% sodium chloride solution equal to the volume of the ACTEMRA solution required for the patient's dose, and discard. Withdraw the required amount of ACTEMRA (0.4 mL per kg of the patient's body weight) under aseptic conditions and add to the infusion bag. To mix the solution, gently invert the bag to avoid foaming.

#### ***pJIA and sJIA patients $\geq$ 30 kg***

From a 100 mL infusion bag, withdraw a volume of 0.9% sodium chloride solution equal to the volume of the ACTEMRA solution required for the patient's dose. Withdraw the required amount of ACTEMRA (0.4 mL per kg of the patient's body weight) under aseptic conditions and dilute in a 100 mL infusion bag containing sterile, non-pyrogenic 0.9% sodium chloride solution. To mix the solution, gently invert the bag to avoid foaming.

#### ***pJIA patients < 30 kg***

From a 50 mL infusion bag, withdraw a volume of 0.9% sodium chloride solution equal to 0.5 mL/kg of the patient's body weight and discard. This volume should be replaced in the saline bag with an equal volume of ACTEMRA under aseptic conditions. To mix the solution, gently invert the bag to avoid foaming.

#### ***sJIA patients < 30 kg***

From a 50 mL infusion bag, withdraw a volume of 0.9% sodium chloride solution equal to 0.6 mL/kg of the patient's body weight and discard. This volume should be replaced in the saline bag with an equal volume of ACTEMRA under aseptic conditions. To mix the solution, gently invert the bag to avoid foaming.

#### ***Solution for Subcutaneous Injection***

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

ACTEMRA should not be shaken.

After removing the pre-filled syringe from the refrigerator, it should be allowed to reach room temperature by waiting for 25 to 30 minutes, before injecting. After removing the cap the injection should be started within 5 minutes.

## **OVERDOSAGE**

There are limited data available on overdosage with ACTEMRA. 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.

Treatment of overdose should consist of general supportive measures.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

## **PRESENTATION AND STORAGE**

### **Concentrated solution for intravenous infusion**

ACTEMRA is available as:

\*(not marketed)

- Single use vial containing 80 mg of ACTEMRA in 4 mL (20 mg/mL). Packs of 1 and 4\* vials.
- Single use vial containing 200 mg of ACTEMRA in 10 mL (20 mg/mL). Packs of 1 and 4\* vials.
- Single use vial containing 400 mg of ACTEMRA in 20 mL (20 mg/mL). Packs of 1 and 4\* vials.

Store vials at 2°C to 8°C. (Refrigerate. Do not freeze.) Keep the container in the outer carton in order to protect from light.

ACTEMRA does not contain any antimicrobial agent; therefore care must be taken to ensure the sterility of the prepared solution. Product is for single use in one patient only. Discard any residue.

The prepared infusion solution of ACTEMRA is physically and chemically stable in 0.9% w/v sodium chloride solution at 30°C for 24 hours. To reduce microbiological hazard, the prepared infusion should be used immediately. If storage is necessary, hold at 2°C – 8°C for not more than 24 hours.

Do not use after the expiry date (EXP) shown on the pack.



### **Solution for subcutaneous injection**

ACTEMRA is available as:

- Single-use pre-filled syringe with needle safety device. Each syringe contains 162 mg of ACTEMRA in 0.9 mL. Packs of 1 and 4 syringes.

Store the pre-filled syringe at 2 °C to 8 °C. (Refrigerate. Do not freeze.) Keep in carton to protect from light and keep dry.

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

ACTEMRA does not contain any antimicrobial agent. Product is for single use in one patient only. Discard any residue.

The medicine should not be used after the expiry date (EXP) shown on the pre-filled syringe and the carton.

### **Disposal of Medicines**

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

### **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 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.

## **NAME AND ADDRESS OF THE SPONSOR**

Roche Products Pty Limited  
ABN 70 000 132 865  
4- 10 Inman Road  
Dee Why NSW 2099  
AUSTRALIA

Medical enquiries: 1800 233 950



**POISON SCHEDULE OF THE MEDICINE**

Prescription Only Medicine (S4)

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER  
OF THERAPEUTIC GOODS (THE ARTG)**

21 May 2009

**DATE OF MOST RECENT AMENDMENT**

21 January 2016