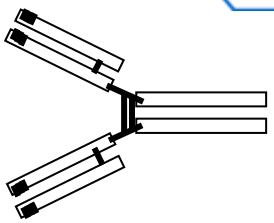
Attachment 1: Product information for AusPAR Actemra Tocilizumab (rch) Roche Products PM-2013-02398-1-3 Date of Finalisation 13 January 2015 This Product Information was approved at the time this AusPAR was published.

ACTEMRA

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 of 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 is a clear to opalescent, colourless to pale yellow sterile solution for intravenous (IV) infusion. 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.

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

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 (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 35000 ± 15500 h·µg/mL, 9.74 ± 10.5 µg/mL, and 183 ± 85.6 µg/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 ≥ 100 kg, the predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 55500 ± 14100 h·µg/mL, 19.0 ± 12.0 µg/mL, and 269 ± 57 µg/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 ≥ 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 (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 13000 ± 5800•µg•h/mL, 1.49 ± 2.13 µg/mL, and 88.3 ± 41.4 µg/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}.

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 ≥ 30 kg) given every 4 weeks. The predicted mean (± SD) AUC_{4weeks}, C_{max} and C_{min} of tocilizumab were 29500 ± 8660 µg•hr/mL, 182 ± 37 µg/mL and 7.49 ± 8.2 µg/mL, respectively.

The following parameters are valid for a dose of 10 mg/kg tocilizumab (patients with a body weight < 30 kg) given every 4 weeks. The predicted mean (± SD) AUC_{4weeks}, C_{max} and C_{min} of tocilizumab were 23200 ± 6100 µg•hr/mL, 175 ± 32 µg/mL and 2.35 ± 3.59 µg/mL, respectively.

The accumulation ratios were 1.05 and 1.16 for AUC_{4weeks}, and 1.43 and 2.22 for C_{min} for 10 mg/kg (body weight (BW) < 30 kg) and 8 mg/kg (BW ≥ 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 ≥ 30 kg) or 12 mg/kg (patients with a body weight < 30 kg), given every 2 weeks. The predicted mean (± SD) AUC_{2weeks}, C_{max} and C_{min} of tocilizumab were 32200 ± 9960 µg•hr/mL, 245 ± 57.2 µg/mL and 57.5 ± 23.3 µg/mL, respectively. The accumulation ratio for C_{min} (week12/week2) was 3.2 ± 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 and Bioavailability
Not applicable.

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.

Elimination

The total clearance of tocilizumab was concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 12.5 mL/h in RA patients, 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, 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.

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 ³ 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 rheumatoid arthritis 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 ACTEMRA in alleviating the signs and symptoms of rheumatoid arthritis was assessed in five randomised, double-blind, multicentre studies. Studies I-V required patients ≥ age 18 with active rheumatoid arthritis 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 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)

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

In all studies, 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 durable 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 MTX Naïve		**Study II Inadequate Response to MTX**		**Study III Inadequate Response to MTX**		**Study IV Inadequate Response to DMARD**		**Study V Inadequate Response to anti-TNF Agent**	
	ACT 8 mg/kg n=286	**MTX n=284**	**ACT 8 mg/kg +MTX n=398**	**Placebo + MTX n=393**	**ACT 8 mg/kg +MTX n=205**	**Placebo + MTX n=204**	**ACT 8 mg/kg + DMARD n=803**	**Placebo + DMARD n=413**	**ACT 8 mg/kg +MTX n=170**	**Placebo +MTX n=158**
Change in DAS28 [mean (Adjusted mean (SE))]										
Week 24	-3.31 (0.12)	-2.05 (0.12)	-3.11 (0.09)***	-1.45 (0.11)	-3.43 (0.12)***	-1.55 (0.15)	-3.17 (0.07)***	-1.16 (0.09)	-3.16 (0.14) ***	-0.95 (0.22)
DAS < 2.6 response (%)										
Week 24	33.6%	12.1%	≠33.3% ***	^3.8%	27.5%***	0.8%	30.2%***	3.4%	30.1% ***	1.6%
EULAR response (%)										
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.

Major Clinical Response

After 2 years of treatment with 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 3).

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 3 Radiographic mean changes at 52 and 104 weeks in study II (LITHE)

	ACT 8 mg/kg + MTX [n=398]	**Placebo + MTX (+ option of ACT from week 16) [n=393]**
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.

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. 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 (≥ 0.3 units) at weeks 52 & 104 were 63% and 62%, 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 naive, Early RA

Study VI (WA19926), 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 ≤ 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 rheumatoid arthritis. This study evaluated the efficacy of 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 (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 VI (WA19926) are shown in Table 4.

Table 4 Efficacy Results for Study VI (WA19926) on MTX-naïve, early RA patients

			ACT 8 mg/kg + MTX n=290	ACT 8 mg/kg + placebo n=292	Placebo + MTX n=287
Primary Endpoint					
DAS < 2.6 response (%)					
Week 24			44.8***	38.7***	15.0
Key Secondary Endpoints					
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
Radiographic Endpoints (mean change from baseline)					
Week 52		mTSS[#]	0.08***	0.26	1.14
		Erosion Score	0.05**	0.15	0.63
		JSN	0.03	0.11	0.51
		Radiographic non-progression (%) (change from baseline in mTSS[#] of ≤ 0)	83[‡]	82[‡]	73

All efficacy comparisons vs Placebo + MTX. ***p ≤ 0.0001; **p < 0.001; *p < 0.05;
[#] mTSS = modified Total Sharp score

Monotherapy: ACTEMRA versus adalimumab

Study WA19924 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 5).

Table 5 Efficacy Results for Study WA19924

	ADA + Placebo (IV) n = 162	ACT + Placebo (SC) n = 163	p-value[(a)]
Primary Endpoint - Mean Change from baseline at Week 24			
DAS28 (adjusted mean)	-1.8	-3.3	
Difference in adjusted mean (95% CI)	-1.5 (-1.8, -1.1)		<0.0001
Secondary Endpoints - Percentage of Responders at Week 24 [(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

[a] *p* value is adjusted for region and duration of RA for all endpoints and additionally baseline value for all continuous endpoints.
[b] Non-responder Imputation used for missing data. Multiplicity controlled using Bonferroni-Holm Procedure

Polyarticular Juvenile Idiopathic Arthritis

The efficacy of 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. 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 6 JIA ACR response rates at week 40 relative to baseline (percentages of patients)

Response Rate	ACTEMRA n=82	Placebo n=81
JIA ACR 30	74.4%†	54.3%†
JIA ACR 50	73.2%†	51.9%†
JIA ACR 70	64.6%†	42.0%†

† 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 7).

Table 7 Proportion of patients with a JIA ACR30 Flare at Week 40 by background MTX use at baseline or prior biologic DMARD use

	placebo		ACTEMRA	
MTX Use	**Yes (n = 64)**	**No (n = 17)**	**Yes (n = 67)**	**No (n = 15)**
JIA ACR30 Flare	25 (39.1%)	14 (82.4%)	13 (19.4%)	8 (53.3%)
Prior Biologic Use	**Yes (n = 23)**	**No (n = 58)**	**Yes (n = 27)**	**No (n = 55)**
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 ACTEMRA for the treatment of active sJIA was assessed in a 12-week randomised, double blind, placebo-controlled, parallel group, 2-arm study. 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 ≥ 30kg 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 ≥ 37.5°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 8 JIA ACR response rates at week 12 (percent of patients)

Response Rate	ACTEMRA n=75	Placebo n=37
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 ≥ 37.5°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 ≥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 ≥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

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

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
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

Serious hypersensitivity reactions, including anaphylaxis with fatal outcome, have been reported in association with infusion of ACTEMRA (see ADVERSE EFFECTS – Infusion Reactions). In the post-marketing setting, events of serious hypersensitivity and anaphylaxis, including in some cases with a fatal outcome, have occurred in patients treated with a range of doses of ACTEMRA, with or without concomitant arthritis therapies, premedication and/or a previous hypersensitivity reaction. 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 treatment with ACTEMRA. 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 to 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 x ULN. In patients with baseline ALT or AST > 5 x ULN, treatment with ACTEMRA is not recommended.
ALT and AST levels should be monitored in RA 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 x ULN, confirmed by repeat testing, ACTEMRA treatment should be interrupted. Once the patient's hepatic transaminases are below 3 x ULN, treatment with ACTEMRA may recommence at 4 or 8 mg/kg.

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 x 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 x 10^9/L). In patients with an ANC < 0.5 x 10^9/L or a platelet count < 50 x 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.

Neutrophils and platelets should be monitored in RA 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.

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

This medicinal product 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'.

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 ACTEMRA 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.

Use in Children

The safety and efficacy of 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 ACTEMRA in children with pJIA who have had an inadequate response to or intolerance to MTX. Long-term safety data for 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.

Use in the Elderly

Population analyses evaluated the potential effects of demographic characteristics on the pharmacokinetics of ACTEMRA in adult rheumatoid arthritis 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.

Carcinogenicity

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

Genotoxicity

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

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 x 10^9/L occurred in 3.4%, with counts < 0.5 x 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 x 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

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 ≥ 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 9 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

All Control Study Population

Preferred Term	ACTEMRA 8 mg/kg monotherapy n=288 (%)	MTX n=284 (%)	ACTEMRA 4 mg/kg + MTX n=774 (%)	ACTEMRA 8 mg/kg + DMARDs n=1870 (%)	Placebo + DMARDs n=1555 (%)
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 rheumatoid arthritis 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 lymphaticsystem 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 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.

In the 6 month controlled clinical trials, the rate of anaphylactic reactions in those receiving the lower dose of 4 mg/kg was 3/744 (0.4%) and in the higher dose of 8 mg/kg was 3/1870 (0.2%). As anaphylactic reactions tend to occur early in the course of treatment, the overall rate of anaphylaxis cumulatively in the long term extensions remained at 6/3778 or 0.2%.

Clinically significant hypersensitivity reactions associated with ACTEMRA and requiring treatment discontinuation, were reported in a total of 13 out of 3778 patients (0.3%) treated with ACTEMRA during the controlled and open label clinical trials. These reactions were generally observed during the second to fifth infusions of ACTEMRA.

Immunogenicity

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

Early Rheumatoid Arthritis

Study VI (WA19926) evaluated 1162 patients with early, moderate to severe RA who were naïve to treatment with both MTX and a biologic agent. The overall safety profile observed in the 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.

Monotherapy: ACTEMRA vs adalimumab

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.

Polyarticular Juvenile Idiopathic Arthritis

The safety of 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 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 ACTMERA 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

In the 6 month controlled trials decreases in neutrophil counts below 1 x 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 x 10^9/L did so within 8 weeks after starting therapy. Decreases below 0.5 x 10^9/L were reported in 0.3% patients receiving ACTEMRA 8 mg/kg + DMARD (see PRECAUTIONS – Effects on Laboratory Tests).

There was no clear relationship between decreases in neutrophils below 1 x 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.

Platelets
In the 6 month controlled trials, decreases in platelet counts below 100 x 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.

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

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

Systemic Juvenile Idiopathic Arthritis
Neutrophils
During routine laboratory monitoring in the 12 week controlled trial, a decrease in neutrophil counts below 1 × 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 x 10^9/L occurred in 15% of patients in the ACTEMRA group.

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

Platelets
During routine laboratory monitoring in the 12 week controlled trial, 3% of patients in the placebo group and 1% in the ACTEMRA group had a decrease in platelet count to ≤ 100 × 10^3/μL. In the ongoing open-label extension study decreases in platelet counts below 100 x 10^3/μL occurred in 3% of patients in the ACTEMRA group, without associated bleeding events.

Liver enzyme elevations

Rheumatoid Arthritis

During the 6 month controlled trials transient elevations in ALT (alanine transaminase)/AST (aspartate transaminase) > 3 x 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 > 5x 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 > 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 VI (WA19926), MTX-naïve adult patients with moderate to severe, active early RA (mean disease duration ≤ 6 months) experienced more transient elevations in ALT > 3 x ULN compared with the *all control* population. Transient elevations in ALT > 3 to 5 x 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.

Polyarticular Juvenile Idiopathic Arthritis

During routine laboratory monitoring in the ACTEMRA all exposure population, elevation in ALT or AST ≥ 3 x ULN occurred in 3.7% and <1% of patients, respectively.

Systemic Juvenile Idiopathic Arthritis

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

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

Elevations in lipid parameters

Rheumatoid Arthritis

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 ≥ 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.

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 ≥ 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 ≥ 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 ACTEMRA treatment (see CONTRAINDICATIONS and PRECAUTIONS – Hypersensitivity Reactions).

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

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.

ACTEMRA should be diluted by a healthcare professional with sterile 0.9% w/v sodium chloride solution using aseptic technique (see section Preparing the Infusion).

ACTEMRA is recommended for IV infusion 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.

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).

Rheumatoid Arthritis in Adults

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).

The calculated dose of ACTEMRA should be diluted to 100 mL and administered as an IV infusion over a period of 1 hour.

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

Dose Modification Recommendations for RA

- Liver enzyme abnormalities

Lab Value	Action
> 1 to 3 x ULN	Dose modify concomitant DMARDs if appropriate For persistent increases in this range, reduce ACTEMRA dose to 4 mg/kg or interrupt ACTEMRA until ALT/AST have normalised Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate
> 3 to 5 x ULN (confirmed by repeat testing, see PRECAUTIONS - Hepatic Transaminase Elevations)	Interrupt ACTEMRA dosing until < 3 x ULN and follow recommendations above for > 1 to 3 x ULN For persistent increases > 3 x ULN, discontinue ACTEMRA
> 5 x ULN	Discontinue ACTEMRA

- Low absolute neutrophil count (ANC)

Lab Value (cells x 10^9/L)	Action
ANC > 1	Maintain dose
ANC 0.5 to 1	Interrupt ACTEMRA dosing When ANC > 1 x 10^9/L resume ACTEMRA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
ANC < 0.5	Discontinue ACTEMRA

- Low platelet count

Lab Value (cells x 10^9/L)	Action
50 to 100	Interrupt ACTEMRA dosing When platelet count is > 100 x 10^9/L resume ACTEMRA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
< 50	Discontinue ACTEMRA

Polyarticular Juvenile Idiopathic Arthritis (pJIA)
The recommended dose of ACTEMRA for patients with pJIA is:

- 10 mg/kg for patients < 30 kilograms,
- 8 mg/kg for patients ≥ 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.

Systemic Juvenile Idiopathic Arthritis (sJIA)
The recommended dose of ACTEMRA for patients with sJIA is:

- 12 mg/kg for patients < 30 kilograms,
- 8 mg/kg for patients ≥ 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.

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.

Preparing the 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 ≥ 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.

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. 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, 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

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 2ºC – 8ºC. (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 30ºC for 24 hours. To reduce microbiological hazard, the prepared infusion should be used immediately. If storage is necessary, hold at 2ºC – 8ºC for not more than 24 hours.
Do not use after the expiry date (EXP) shown on the pack.

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.

POISON SCHEDULE

Prescription Only Medicine (S4)

Attachment 1: Product information for AusPAR Actemra Tocilizumab (rch) Roche Products PM-2013-02398-1-3 Date of Finalisation 13 January 2015 This Product Information was approved at the time this AusPAR was published.

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

21 May 2009

DATE OF MOST RECENT AMENDMENT

14 October 2014