ACTEMRA® (TOCILIZUMAB) FOR THE INDICATIONS OF THE FOLLOWING:

- Rheumatoid Arthritis [Intravenous]
- Polyarticular Juvenile Idiopathic Arthritis [Intravenous]
- Systemic Juvenile Idiopathic Arthritis (Intravenous)

IMPORTANT EFFICACY AND SAFETY INFORMATION

To assist healthcare professionals in assessing the benefits and risks associated with Actemra **therapy in patients with rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA) and systemic juvenile idiopathic arthritis (sJIA).**

Healthcare professionals are asked to report any suspected adverse reactions. See final page for details on how to report.

This educational material is mandatory as a condition of the marketing authorisation of intravenous Actemra in order to further minimise important selected risks.

Table of Content

1. Indications and usage

1.1 Rheumatoid Arthritis (RA) [Intravenous]

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

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

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

Actemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with MTX.

1.2 Juvenile Idiopathic Polyarthritis (pJIA) [Intravenous]

Actemra in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX.

Actemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate

1.3 Systemic Juvenile Idiopathic Arthritis (sJIA) [Intravenous]

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

Actemra can be given as monotherapy (in case of intolerance to methotrexate [MTX] or where treatment with MTX is inappropriate) or in combination with MTX.

2. Patient counselling information

Before initiating therapy, patients and parents/guardians of RA, pJIA and sJIA patients should be advised of the potential risks and benefits of Actemra.

The risks associated with Actemra treatment include:

2.1 Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including Actemra. Inform patients and parents/guardians of RA, pJIA, sJIA patients that Actemra may lower the patient's resistance to infections. Instruct the patient and their parents/guardians to **seek immediate medical attention** if signs or symptoms suggesting infection appear in order to ensure rapid evaluation and appropriate treatment. Signs or symptoms of infection may include:

- Fever
- Persistent cough
- Weight loss
- Throat pain or soreness
- Wheezing
- Red or swollen skin blisters, skin tears or wounds
- Severe weakness or tiredness

2.2 Hypersensitivity Reactions

Inform the patient and parents/guardians of the patient that serious allergic reactions including anaphylaxis have been reported in association with Actemra IV. Such reactions may be more severe, and potentially fatal, in patients who have experienced allergic reactions during previous treatment with Actemra even if they have received premedication with steroids and antihistamines. Most allergic reactions occur during infusion/injection or within 24 hours of Actemra administration, although allergic reactions can occur at any time.

Fatal anaphylaxis has been reported during treatment with intravenous Actemra.

Instruct the patient and their parents/guardians to **seek immediate medical attention** if signs or symptoms suggesting a systemic allergic reaction appear in order to ensure rapid evaluation and appropriate treatment. Possible signs or symptoms of a systemic allergic reaction include:

- Rash, itching or hives
- Shortness of breath or trouble breathing
- Swelling of the lips, tongue or face
- Chest pain
- Feeling dizzy or faint
- Severe stomach pain or vomiting
- Hypotension

During the Actemra IV infusion, watch the patient closely for any signs and symptoms of hypersensitivity, including anaphylaxis.

If an anaphylactic reaction or other serious hypersensitivity reaction occurs, Actemra IV administration should be stopped immediately, appropriate therapy initiated and Actemra should be permanently discontinued.

Instruct the patients or the parents/guardians of RA, pJIA and patients who are administering Actemra **to seek immediate medical attention** if they or their child experience any symptoms suggestive of an allergic reaction and **not** give the next dose until they have informed their doctor **AND** their doctor has told them to give the next dose if they or their child has experienced any allergic reaction symptoms after receiving Actemra.

2.3 Vaccinations

Inform patients and parents/guardians of patients that patients should not receive any live or live-attenuated vaccines during Actemra therapy. Patients should 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.

2.4 Gastrointestinal side effects

Inform patients and parents/guardians of patients that some patients who have been treated with Actemra have had serious side effects in the stomach and intestines. **Instruct the** patients and parents/guardians of patients **to seek immediate medical attention** if signs or symptoms of severe, persistent abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever appear, to ensure rapid evaluation and appropriate treatment.

Before you administer Actemra, ask the the patient or parents/guardians of the patients if they:

- Have an infection, are being treated for an infection or have a history of recurring infections
- Have signs of an infection, such as a fever, cough or headache, or are feeling unwell
- Have herpes zoster or any other skin infection with open sores
- Have had any allergic reactions to previous medications, including Actemra
- Have diabetes or other underlying conditions that may predispose him or her to infection
- Have tuberculosis (TB), or have been in close contact with someone who has had TB
  - As recommended for other biologic therapies in rheumatoid arthritis, patients should be screened for latent TB infection prior to starting Actemra therapy. Patients with latent TB should be treated with standard antimycobacterial therapy before initiating Actemra
- Are taking other biological drugs to treat RA, or receiving atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporine or benzodiazepines
- Have had or currently have viral hepatitis or any another hepatic disease

- Have a history of gastrointestinal ulcers or diverticulitis
- Have recently received a vaccination or are scheduled for any vaccination
- Have cancer, cardiovascular risk factors such as raised blood pressure and raised cholesterol levels or moderate-to-severe kidney function problems
- Have persistent headaches.

Patients who are young woman of childbearing potential, may become pregnant or sexually active, or might be pregnant, intend to become pregnant, or are breast-feeding must use effective contraception during (and up to 3 months after) treatment. Actemra should not be used during pregnancy unless absolutely necessary.

2.5 Macrophage activation syndrome (MAS)

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

MAS is a well-recognised and potentially life-threatening complication of sJIA with an estimated incidence in patients with sJIA of between 7% and 13%1,2 and a reported mortality rate of 8% to 22%.[1,3]

MAS is thought to be triggered by infections or changes in medications, but MAS can occur without clear reasons or aetiology.[1]

Diagnosis of MAS
There are currently no universally accepted definitive diagnostic criteria although preliminary criteria have been published.[4]

The differential diagnosis of MAS is broad because of the variable and multi-system abnormalities of the disorder and the non-specific nature of the most prominent clinical features, which include fever, hepatosplenomegaly and cytopenia. As a result, achieving a rapid clinical diagnosis is often difficult. Other features of MAS include neurologic abnormalities, and laboratory abnormalities including hypofibrinogenaemia. Successful treatment of MAS has been reported with ciclosporin and glucocorticoids.

The severity and life-threatening nature of this complication, coupled with the frequent difficulties in achieving a rapid diagnosis, necessitate appropriate vigilance and careful management of patients with active sJIA.

IL-6 inhibition and MAS
Some of the laboratory features associated with Actemra administration related to IL-6 inhibition are similar to some of the laboratory features associated with the diagnosis of MAS (such as a decline in leukocyte count, neutrophil count, platelet count, serum fibrinogen and erythrocyte sedimentation rate, all of which occur most notably within the week following

Actemra administration). Ferritin levels frequently decrease with Actemra administration, but often increase with MAS and, therefore, may be a useful differential laboratory parameter.

Characteristic clinical findings of MAS (central nervous system dysfunction, haemorrhage and hepatosplenomegaly), if present, are useful in establishing the diagnosis of MAS in the context of IL-6 inhibition. Clinical experience and the clinical status of the patient, coupled with the timing of the laboratory specimens in relation to Actemra administration, must guide interpretation of these laboratory data and their potential significance in making a diagnosis of MAS.

In clinical trials, Actemra has not been studied in patients during an episode of active MAS.

2.6 Laboratory monitoring by indication

2.6.1 Laboratory monitoring for RA

Neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. Lipids should be monitored 4 to 8 weeks following initiation of Actemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

2.6.1.1 Neutrophils

Decreases in neutrophil counts have occurred following treatment with Actemra 8 mg/kg IV once every 4 weeks in combination with DMARDs.
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. In patients who develop an ANC <0.5 x 10^9/l, continued treatment is not recommended.
Severe neutropenia may be associated with an increased risk of serious infections, although there has been no clear association established in clinical trials with Actemra to date. Infections have been reported in patients with neutropenia in clinical trials.
Neutrophils should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice.

Low absolute neutrophil count (ANC)

Laboratory value (cells x 10^9/l)	Action
ANC >1	Maintain dose
ANC 0.5 to 1	**Actemra IV**
	Interrupt Actemra dosing When ANC increases >1 x 10^9/ l resume Actemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate

ANC <0.5	Discontinue Actemra

2.6.1.2 Platelets

Decreases in platelet counts have occurred following treatment with Actemra 8 mg/kg IV once every four weeks in combination with DMARDs.

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

Platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice.

Low platelet count

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

2.6.1.3 Hepatic transaminases

In clinical trials, transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with Actemra treatment, without progression to hepatic injury. An increased frequency of these elevations was observed when potential hepatotoxic drugs (e.g., MTX) were used in combination with Actemra. When clinically indicated, other liver function tests including bilirubin should be considered.

Caution should be exercised when considering initiation of Actemra treatment in patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5 x upper limit of normal (ULN). In patients with baseline ALT or AST >5 x ULN, treatment is not recommended.

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 ALT or AST elevations >3 to 5 x ULN, Actemra treatment should be interrupted.

Liver enzyme abnormalities

Laboratory value	Action
>1 to 3 x ULN	**Actemra IV**
	Modify the dose of the concomitant MTX if appropriate For persistent increases in this range, reduce Actemra dose to 4 mg/kg or interrupt Actemra until ALT or AST have normalised Restart with 4 mg/kg or 8 mg/kg, 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. For persistent increases >3 x ULN (confirmed by repeat testing), discontinue Actemra
>5 x ULN	Discontinue Actemra.

2.6.1.4 Lipids

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

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

2.6.2 Laboratory monitoring for pJIA (IV)

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and neutrophils and platelets should be monitored at the time of the second infusion and thereafter according to good clinical practice (see section *Warning and Precautions, Laboratory parameters*).

Assessment of lipid parameters should be performed 4 to 8 weeks following initiation of Actemra therapy (see section *Warning and Precautions, Laboratory parameters*). Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

Reduction of tocilizumab dose due to laboratory abnormalities has not been studied in pJIA patients.

Dose interruptions of tocilizumab for the following laboratory abnormalities are recommended in pJIA patients in the tables below. If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and tocilizumab dosing interrupted until the clinical situation has been evaluated. As there are many co-morbid conditions that may effect

laboratory values in pJIA, the decision to discontinue tocilizumab for a laboratory abnormality should be based upon the medical assessment of the individual patient.

2.6.2.1 Neutrophils

Low absolute neutrophil count (ANC)

Laboratory value (cells x 10^9/l)	Action
ANC >1	Maintain dose
ANC 0.5 to 1	**Actemra IV**
	Interrupt Actemra dosing When ANC increases to > 1 x 10^9/ l resume Actemra
ANC <0.5	Discontinue Actemra The decision to discontinue Actemra in pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

2.6.2.2 Platelets

Low platelet count

Laboratory value (cells x 10^3/µl)	Action
50 to 100	**Actemra IV**
	Modify the dose of the concomitant MTX if appropriate. Interrupt Actemra dosing When platelet count is > 100 x 10^3/µl resume Actemra
<50	Discontinue Actemra: The decision to discontinue Actemra in pJIA for a laboratory abnormality should be based on the medical assessment of the individual patient.

2.6.2.3 Hepatic Transaminases

In clinical trials, transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with Actemra treatment, without progression to hepatic injury. An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with Actemra. When clinically indicated, other liver function tests including bilirubin should be considered.

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 is not recommended.

For recommended modifications based on transaminases see table below. For ALT or AST elevations > 3–5 x ULN, Actemra treatment should be interrupted.

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

Liver enzyme abnormalities

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

2.6.2.4 Lipids

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

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

2.6.3 Laboratory monitoring for sJIA (IV)

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and neutrophils and platelets should be monitored at the time of the second infusion and thereafter according to good clinical practice (see section *Warning and Precautions, Laboratory parameters*).

Assessment of lipid parameters should be performed 4 to 8 weeks following initiation of Actemra therapy (see section *Warning and Precautions, Laboratory parameters*).

2.6.3.1 Neutrophils

Decreases in neutrophil counts have occurred following treatment with Actemra. 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. In patients who develop an ANC <0.5 x 10^9/l, continued treatment is not recommended. Severe neutropenia may be associated with an increased risk of serious infections. Infections have been reported in neutropenic patients. Neutrophils should be monitored at the time of second infusion and thereafter according to good clinical practice.

Low absolute neutrophil count (ANC)

Laboratory value (cells x 10^9/l)	Action
ANC >1	Maintain RoACTEMRA dose
ANC 0.5 to 1	Interrupt RoACTEMRA dosing When ANC increases to >1 x 10^9/l resume RoACTEMRA
ANC <0.5	Discontinue RoACTEMRA The decision to discontinue RoACTEMRA for a laboratory abnormality should be based on the medical assessment of the individual patient

2.6.3.2 Platelets

Decrease in platelet counts have occurred following treatment with Actemra.

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

Platelets should be monitored at the time of second infusion and thereafter according to good clinical practice.

Low platelet count

Laboratory value (cells x 10^3/µl)	Action
	Modify the dose of the concomitant MTX if appropriate
50 to 100	Interrupt RoACTEMRA dosing
	When platelet count is >100 x 10^3/µl resume RoACTEMRA
	Discontinue RoACTEMRA
<50	The decision to discontinue RoACTEMRA for a laboratory abnormality should be based on the medical assessment of the individual patient

2.6.3.3 Hepatic transaminases

In clinical trials, transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with Actemra treatment, without progression to hepatic injury. An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. MTX) were used in combination with Actemra. When clinically indicated, other liver function tests including bilirubin should be considered.

Caution should be exercised when considering initiation of Actemra treatment in patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5 x upper limit of normal (ULN). In patients with baseline ALT or AST >5 x ULN, treatment is not recommended.

ALT and AST levels should be monitored at the time of the second infusion and thereafter according to good clinical practice. For ALT or AST elevations >3 to 5 x ULN, Actemra treatment should be interrupted.

Liver enzyme abnormalities

Laboratory Value	Action
	Modify the dose of the concomitant MTX if appropriate
>1 to 3 x ULN	For persistent increases in this range, interrupt RoACTEMRA until ALT/AST have normalised
	Modify the dose of the concomitant MTX if appropriate
>3 to 5 x ULN	Interrupt RoACTEMRA dosing until <3 x ULN and follow recommendations above for >1 to 3 x ULN
	Discontinue RoACTEMRA
>5 x ULN	The decision to discontinue RoACTEMRA for a laboratory abnormality should be based on the medical assessment of the individual patient

2.6.3.4 Lipids

Elevations in lipid parameters including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were observed in patients treated with Actemra. Assessment of lipid parameters should be performed 4 to 8 weeks following initiation of

Actemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

3. Clinical response

The potential benefits associated with Actemra treatment described below by indication:

3.1 RA

The potential benefits associated with Actemra treatment in RA

3.1.1 Actemra IV

The percentages of patients achieving ACR20, ACR50 and ACR70 are shown below. In all studies, patients treated with 8 mg/kg Actemra had statistically significant ACR20, ACR50 and ACR70 response rates versus MTX- or placebo-treated patients at Week 24. Some patients experienced ACR20 responses as early as 2 weeks for the Actemra doses studied.

ACR responses in placebo-/MTX-/DMARD-controlled studies (percent of patients)

	Study I AMBITION		Study II LITHE		Study III OPTION		Study IV TOWARD		Study V RADIATE	
Week	TCZ 8 mg/kg	MTX	TCZ 8 mg/kg + MTX	Placebo + MTX	TCZ 8 mg/kg + MTX	Placebo + MTX	TCZ 8 mg/kg + DMARD	Placebo + DMARD	TCZ 8 mg/kg + MTX	Placebo + MTX
	n=286	n=284	n=398	n=393	n=205	n=204	n=803	n=413	n=170	n=158
					ACR 20					
24	70%***	52%	56%***	27%	59%***	26%	61%***	24%	50%***	10%
52			56%***	25%						
					ACR 50					
24	44%**	33%	32%***	10%	44%***	11%	38%***	9%	29%***	4%
52			36%***	10%						
					ACR 70					
24	28%**	15%	13%***	2%	22%***	2%	21%***	3%	12%**	1%
52			20%***	4%						

TCZ = Tocilizumab
MTX = Methotrexate
DMARD = Disease-modifying anti-rheumatic drug
** p<0.01, TCZ vs. Placebo + MTX/DMARD
*** p<0.0001, TCZ vs. Placebo + MTX/DMARD

Patients in Studies I to V had a mean Disease Activity Score (DAS28) of 6.5 to 6.8 at baseline. Significant reductions in DAS28 from baseline (mean improvement) of 3.1 to 3.4 were observed in Actemra-treated patients compared with control patients (1.3–2.1). The proportion of patients achieving a DAS28 clinical remission (DAS28 <2.6) was significantly higher in patients receiving Actemra (28% to 34%) compared with 1% to 12% of control patients at 24 weeks. In Study II, 65% of patients achieved a DAS28 <2.6 at 104 weeks compared with 48% at 52 weeks and 33% at Week 24.

Actemra versus adalimumab in monotherapy

In a 24-week study evaluating 326 patients with RA who were intolerant of MTX or where continued treatment with MTX was considered inappropriate (including MTX-inadequate responders), a superior treatment effect was seen in favour of Actemra monotherapy over adalimumab (ADA) monotherapy. The change in DAS28, a measure of control of disease activity, and all secondary endpoints were in favour of Actemra monotherapy (Table below).

Efficacy results favouring tocilizumab monotherapy

	ADA + Placebo (IV) n = 162	TCZ + 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 (%)	17 (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

3.2 PJIA

The potential benefits associated with Actemra treatment in pJIA

CHERISH study
In the CHERISH study, 48.1% (39/81) of placebo-treated patients and 25.6% (21/82) of Actemra-treated patients developed a JIA ACR30 flare by Week 40 relative to Week 16 (primary endpoint). These proportions were statistically significantly different (p=0.0024). The percentages of patients achieving JIA ACR30, 50 and 70 responses are shown below.
CHERISH: JIA ACR response rates at Week 40 relative to baseline (percent of patients)

Response rate	Actemra n=82	Placebo n=81
JIA ACR30	74.4%*	54.3%*
JIA ACR50	73.2%*	51.9%*
JIA ACR70	64.6%*	42.0%*

* p<0.01, Actemra vs. placebo

The number of active joints was significantly reduced compared with baseline in patients receiving Actemra compared with placebo (p=0.0435), as was the physician's global assessment of disease activity (p=0.0031).

The adjusted mean change in the pain visual analogue scale (VAS) after 40 weeks of Actemra treatment was 32.4 mm on a 0–100 mm scale compared with a reduction of 22.3 mm for placebo patients. This greater reduction in pain on Actemra in comparison with placebo was highly statistically significant (p=0.0076).

3.3 sJIA

The potential benefits associated with Actemra treatment in sJIA

sJIA with Actemra IV

In the TENDER study, 85% (64/75) of Actemra-treated patients and 24% (9/37) of placebo-treated patients achieved the primary endpoint of at least 30% improvement in the JIA ACR core set (JIA ACR30 response) and absence of fever (no temperature recording ≥37.5°C in the preceding 7 days) at Week 12. These proportions were highly significantly different (p<0.0001).

The percentages of patients achieving JIA ACR30, 50, 70 and 90 responses are shown below. Responses are maintained in the ongoing open-label extension phase.

TENDER: JIA ACR response rates at Week 12 (% patients)

Response rate	Tocilizumab n=75	Placebo n=37
JIA ACR30	90.7%*	24.3%
JIA ACR50	85.3%*	10.8%
JIA ACR70	70.7%*	8.1%
JIA ACR90	37.3%*	5.4%

*p<0.0001, tocilizumab vs. placebo

Systemic Effects

In the Actemra-treated patients, 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-treated patients (p<0.0001).

The adjusted mean change in the pain visual analogue scale (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-treated patients (p<0.0001).

Corticosteroid Tapering

Patients achieving a JIA ACR70 response were permitted corticosteroid dose reduction. Seventeen (24%) Actemra-treated patients versus one (3%) placebo-treated patient were able to reduce their corticosteroid dose by at least 20% without experiencing a subsequent JIA ACR30 flare or occurrence of systemic symptoms to Week 12 (p=0.028). Reductions in

corticosteroids continued, with 44 patients off oral corticosteroids at Week 44, while maintaining JIA ACR responses.

Health-related and quality-of-life outcomes

At Week 12, the proportion of Actemra-treated patients showing a minimally clinically important improvement in the Childhood Health Assessment Questionnaire – Disability Index (defined as an individual total score decrease of ≥0.13) was significantly higher than in placebo-treated patients, 77% versus 19% ($p<0.0001$). Laboratory Parameters
In the Actemra-treated patients, 67% (50/75) had a haemoglobin less than the lower limit of normal (LLN) at baseline and 80% (40/50) of these patients had an increase in their haemoglobin to within the normal range at Week 12, in comparison to only 7% (2/29) of placebo-treated patients with haemoglobin <LLN at baseline ($p<0.0001$).

4. Special Warnings and Precautions for Use

4.1 Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including Actemra. Actemra treatment should not be initiated in patients with active infections. Administration of Actemra should be interrupted if a patient develops a serious infection until the infection is controlled. Healthcare professionals should exercise caution when considering the use of Actemra in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes or interstitial lung disease) which may predispose patients to infections.

Vigilance for the timely detection of serious infection is recommended for patients receiving immunosuppressive agents, such as Actemra, as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute-phase reactants. The effects of Actemra on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients (including younger children who may be less able to communicate their symptoms) and parents/guardians of minors should be instructed to contact their healthcare professional immediately if any symptoms suggesting infection appear, in order to ensure rapid evaluation and appropriate treatment.

4.1.1 Tuberculosis

As recommended for other biologic treatments, all patients should be screened for latent TB prior to starting Actemra therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating Actemra. Prescribers 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 and parents/guardians of patients should be advised to **seek medical advice** if signs/symptoms (e.g. persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis (TB) infection occur during or after therapy with Actemra.

4.1.2 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.

4.1.3 Complications of diverticulitis

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

4.2 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported in association with Actemra. Such reactions may be more severe, and potentially fatal in patients who have experienced hypersensitivity reactions during previous treatment with Actemra even if they have received premedication with steroids and antihistamines. Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during treatment with IV Actemra. If an anaphylactic reaction or other serious hypersensitivity reaction/serious infusion related reaction occurs, occurs, administration of Actemra should be stopped immediately, appropriate therapy initiated and Actemra should be permanently discontinued. Fatal anaphylaxis has been reported after marketing authorisation during treatment with intravenous Actemra.

4.3 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. 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 is not recommended.

In RA patients, 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 ALT or AST elevations > 3–5 x ULN, confirmed by repeat testing, Actemra treatment should be interrupted.

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

4.4 Haematological Abnormalities

Decreases in neutrophil and platelet counts have occurred following treatment with Actemra 8 mg/kg in combination with MTX. 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 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 below 100 x 10^3/ µL). In patients who develop an ANC < 0.5 x 10^9/L or a platelet count < 50 x 10^3/µL, continued treatment is not recommended.

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

In RA patients, neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice.

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

4.5 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. 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 4 to 8 weeks following initiation of Actemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia

4.6 Neurological 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.

4.7 Malignancy

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

4.8 Vaccinations

Live and live-attenuated vaccines should not be given concurrently with Actemra as clinical safety has not been established. In a randomized open-label study, adult RA patients treated with Actemra and MTX were able to mount an effective response to both the 23-valent pneumococcal polysaccharide and tetanus toxoid vaccines which was comparable to the response seen in patients on MTX only. It is recommended that all patients, particularly children and elderly patients, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Actemra therapy. The interval between live vaccinations and initiation of Actemra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

4.9 Cardiovascular Risk

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

4.10 Combination with TNF antagonists

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

4.11 Sodium

Actemra IV contains 1.17 mmol (or 26.55 mg) sodium per maximum dose of 1200 mg. To be taken into consideration by patients on a controlled sodium diet. Doses below 1025 mg of this medicinal product contain less than 1 mmol sodium (23 mg), i.e. essentially 'sodium free'.

4.12 Macrophage activation syndrome (MAS) in sJIA

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

4.13 Product traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

5. Undesirable effects

5.1 Summary of the safety profile by indication

5.1.1 RA

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

The most serious ADRs were serious infections, complications of diverticulitis, and hypersensitivity reactions.

5.1.1.1 Actemra IV in RA

5.1.1.1.1 Infections

In the 6-month controlled RA studies, the rate of all infections reported with Actemra 8 mg/kg plus DMARD treatment was 127 events per 100 patient-years compared with 112 events per 100 patient-years in the placebo plus DMARD group. In the long-term exposure population, the overall rate of infections with Actemra was 108 events per 100 patient-years exposure.

In 6-month controlled RA clinical studies, the rate of serious infections with Actemra 8 mg/kg plus DMARDs was 5.3 events per 100 patient-years exposure compared with 3.9 events per 100 patient-years exposure in the placebo plus DMARD group. In the monotherapy study the rate of serious infections was 3.6 events per 100 patient-years of exposure in the Actemra group and 1.5 events per100 patient-years of exposure in the MTX group.

In the long-term exposure RA 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 pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported.

5.1.1.1.2 Other adverse reactions

System Organ Class	Very Common	Common	Uncommon
Blood and lymphatic system disorders		Leukopenia, Neutropenia	
Endocrine disorders			Hypothyroidism
Eye disorders		Conjunctivitis	
Gastrointestinal disorders		Abdominal pain, Mouth ulceration, Gastritis	Stomatitis, Gastric ulcer
General disorders and administration site conditions	Injection site reaction	Peripheral oedema Hypersensitivity reaction	
Infections and infestations	Upper respiratory tract infections	Cellulitis, Pneumonia, Oral herpes simplex, Herpes zoster	Diverticulitis
Investigations		Hepatic transaminases increased, Weight increased, Total bilirubin increased*	
Metabolism and nutrition disorders	Hypercholesterolaemia*		Hypertriglyceridaemia
Nervous system disorders		Headache, Dizziness	
Renal and urinary disorders			Nephrolithiasis
Respiratory, thoracic and mediastinal disorders		Cough, Dyspnoea	
Skin and subcutaneous tissue disorders		Rash, Pruritus, Urticaria	
Vascular disorders		Hypertension	

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

5.1.1.1.3 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 plus DMARD group and 5.1% of patients in the placebo plus DMARD group. Events reported during the infusion were primarily episodes of hypertension; events reported within 24 hours of finishing an infusion were headache and skin reactions (rash, urticaria). These events were not treatment limiting.

The rate of anaphylactic reactions, (occurring in a total of 6 out of 3,778 patients 0.2%), was several-fold higher with the 4 mg/kg dose, compared to the 8 mg/kg dose. Clinically significant

hypersensitivity reactions associated with Actemra and requiring treatment discontinuation were reported in a total of 13 out of 3778 patients (0.3%) treated with Actemra during the controlled and open-label clinical studies. These reactions were generally observed during the second to fifth infusions of Actemra. Fatal anaphylaxis has been reported after marketing authorisation during treatment with Actemra IV.

5.1.1.1.4 Interstitial lung disease

Impaired lung function may increase the risk for developing infections. There have been post-marketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

5.1.1.1.5 Immunogenicity

A total of 2,876 patients have been tested for anti-Actemra antibodies in the 6-month controlled clinical trials. Of the 46 patients (1.6%) who developed anti-Actemra antibodies, 6 had an associated medically significant hypersensitivity reaction, of which 5 led to permanent discontinuation of treatment. Thirty patients (1.1%) developed neutralising antibodies.

5.1.1.1.6 Malignancies

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

5.1.2 PJIA

In general, the most common adverse drug reactions in pJIA patients were similar in type to those seen in Rheumatoid Arthritis (RA) patients.

5.1.2.1 Actemra IV in pJIA

The safety of tocilizumab in pJIA has been studied in 188 patients from 2 to 17 years of age. The total patient exposure was 184.4 patient years. The types of ADRs in pJIA patients were similar to those seen in RA and sJIA patients. When compared to the adult RA population, events of nasopharyngitis, headache, nausea, and decreased neutrophil count were more frequently reported in the pJIA population. Events of cholesterol increased were less frequently reported in the pJIA population than in the adult RA population.

5.1.2.1.1 Infections

The rate of infections in the tocilizumab all exposure population was 163.7 per 100 patient years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was numerically higher in patients weighing <30 kg treated with 10 mg/kg tocilizumab (12.2 per 100 patient years) compared to patients weighing ≥30 kg, treated with 8 mg/kg tocilizumab (4.0 per 100 patient years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing <30 kg treated with 10 mg/kg tocilizumab (21.4%) compared to patients weighing ≥30 kg, treated with 8 mg/kg tocilizumab (7.6%).

5.1.2.1.2 Infusion Reactions

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

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

5.1.2.1.3 Immunogenicity

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

5.1.2.1.4 Neutrophils

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

5.1.2.1.5 Platelets

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

5.1.2.1.6 Hepatic transaminase elevations

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

5.1.2.1.7 Lipid parameters

During routine laboratory monitoring in the Actemra all exposure population, elevation in total cholesterol >1.5-2 x ULN occurred in one patient (0.5%) and elevation in LDL >1.5-2 x ULN in one patient (0.5%).

5.1.3 SJIA

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

In general, the ADRs in sJIA patients were similar in type to those seen in RA patients. When compared to the adult RA population, patients with sJIA experienced a higher frequency of nasopharyngitis, decrease in neutrophil counts, hepatic transaminases increased, and diarrhea. Events of cholesterol increased were less frequently reported in the sJIA population than in the adult RA population.

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

5.1.3.1 Infections

In the 12-week controlled clinical study, the rate of all infections in the Actemra IV group was 344.7 per 100 patient-years compared with 287.0 per 100 patient-years in the placebo group. In the open-label extension study, the overall rate of infections remained similar at 306.6 per 100 patient-years. In this 12-week controlled clinical study, the rate of serious infections in the IV Actemra group was 11.5 per 100 patient-years. In the open-label extension study, the overall rate of serious infections remained stable at 11.3 per 100 patient-years. Reported serious infections were similar to those seen in RA patients with the addition of varicella and otitis media.

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

5.1.3.2 Infusion reactions

In sJIA patients, infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion with IV Actemra. In the 12-week controlled clinical study, 4% 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 Actemra group, 16% of patients experienced an event within 24 hours of infusion compared to 5.4% of patients in the placebo group during the 12-week clinical study. In the Actemra group, the events included, but were not limited to, rash, urticaria, diarrhea, epigastric discomfort, arthralgia and headache. One of these events, urticaria, was considered serious.

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

5.1.3.3 Immunogenicity

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

5.1.3.4 Neutrophils

In sJIA patients, during routine laboratory monitoring in the 12-week clinical study, a decrease in neutrophil counts below 1 x 10^9/l occurred in 7% of patients in the IV Actemra group, and no decreases in the placebo group.

In the open-label clinical study, decreases in neutrophil counts below 1 x 10^9/l occurred in 15% of the IV Actemra group.

In the 52-week clinical trial, neutrophil count decrease below 1 × 10^9/L occurred in 23.5% of patients treated with SC Actemra.

5.1.3.5 Platelets

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

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

5.1.3.6 Hepatic transaminase elevations

During routine laboratory monitoring in the 12-week clinical study in sJIA patients, elevation in ALT or AST ≥3 x ULN occurred in 5% and 3% of patients, respectively, in the IV Actemra group, and none in the placebo group.
In the open-label clinical study, elevation in ALT or AST ≥3 x ULN occurred in 12% and 4% of patients, respectively, in the IV Actemra group.

5.1.3.7 Immunoglobulin G

IgG levels decrease during therapy. A decrease to the LLN occurred in 15 patients at some point in the study.

5.1.3.8 Lipid parameters

During routine laboratory monitoring in the 12-week IV clinical study, 13.4% and 33.3% of patients experienced a post-baseline elevation of their LDL-cholesterol value to ≥ 130 mg/dL and total cholesterol value to ≥ 200 mg/dL, respectively.

6. Drug interactions and other forms of interactions

Interaction studies have only been performed in adults.

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

Population pharmacokinetic analyses did not detect any effect of MTX, non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids on Actemra clearance. In patients, no effect of cumulative corticosteroid dose on Actemra exposure was observed.
Actemra has not been studied in combination with TNF antagonists or other biologic treatments. Actemra is not recommended for use with other biologic agents.

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

7.6 Renal impairment

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

Renal function should be closely monitored in all patients with severe renal impairment and in paediatric patients with moderate-to-severe renal impairment; Actemra has not been studied in these patients.

7.7 Hepatic impairment

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

7.8 Paediatric patients

The safety and efficacy of Actemra IV has not been studied in children below 2 year of age for any indication. In addition, the safety and efficacy of Actemra has not been studied in the below patients:

- RA:
  - Actemra IV : Children below 18 years of age
- pJIA:
  - Actemra IV : Children below 2 years of age
- sJIA:
  - Actemra IV: Children below 2 years of age

Therefore, Actemra is not recommended for use in these children.

8. Dosage and administration

8.1 Actemra IV

8.1.1 RA

The recommended dose of Actemra for adult patients with RA is 8 mg/kg body weight, but no higher than 800 mg, given every 4 weeks as a 1-hour, single-drip IV infusion.

- Actemra can be used concomitantly with MTX or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate
- Actemra has not been studied in combination with TNF antagonists or other biologic treatments for RA. Actemra is not recommended for use with other biologic agents

8.1.2 General dose advice

It is not recommended to initiate Actemra treatment in patients with:

- A low neutrophil count, i.e. absolute neutrophil count (ANC) less than $2x10^9$/l. In patients who develop an ANC <0.5 x 10^9/l, continued treatment is not recommended.

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

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

In a study in RA patients, levels of simvastatin (CYP3A4) were decreased by 57% one week following a single dose of Actemra, to the level similar to, or slightly higher than, those observed 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 or 2C9 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses may need to be increased to maintain therapeutic effect. Given its long elimination half-life ($t_{1/2}$), the effect of Actemra on CYP450 enzyme activity may persist for several weeks after stopping therapy.

7. Use in specific populations

7.1 Pregnancy

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

Actemra should not be used during pregnancy unless clearly necessary.

7.2 Women of childbearing potential

Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

7.3 Breast-feeding

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

7.4 Fertility

Available non-clinical Actemra data do not suggest an effect on fertility.

7.5 Patients Aged 65 Years and Older

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

7.6 Renal impairment

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

Renal function should be closely monitored in all patients with severe renal impairment and in paediatric patients with moderate-to-severe renal impairment; Actemra has not been studied in these patients.

7.7 Hepatic impairment

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

7.8 Paediatric patients

The safety and efficacy of Actemra IV has not been studied in children below 2 year of age for any indication. In addition, the safety and efficacy of Actemra has not been studied in the below patients:

- RA:
  - Actemra IV : Children below 18 years of age
- pJIA:
  - Actemra IV : Children below 2 years of age
- sJIA:
  - Actemra IV: Children below 2 years of age

Therefore, Actemra is not recommended for use in these children.

8. Dosage and administration

8.1 Actemra IV

8.1.1 RA

The recommended dose of Actemra for adult patients with RA is 8 mg/kg body weight, but no higher than 800 mg, given every 4 weeks as a 1-hour, single-drip IV infusion.

- Actemra can be used concomitantly with MTX or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate
- Actemra has not been studied in combination with TNF antagonists or other biologic treatments for RA. Actemra is not recommended for use with other biologic agents

8.1.2 General dose advice

It is not recommended to initiate Actemra treatment in patients with:

- A low neutrophil count, i.e. absolute neutrophil count (ANC) less than $2x10^9$/l. In patients who develop an ANC <0.5 x 10^9/l, continued treatment is not recommended.

- Caution should be exercised when considering initiation of Actemra treatment in patients with a low platelet count (i.e., platelet count below 100 x 10^3/µl). In patients who develop a platelet count <50 x 10^3/µl, continued treatment is not recommended.
- Caution should be exercised when considering initiation of Actemra treatment in patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5 x upper limit of normal (ULN). In patients with baseline ALT or AST >5 x ULN, treatment is not recommended. For ALT or AST elevations >3 to 5 x ULN, Actemra treatment should be interrupted.
- Reduction of dose from 8 mg/kg to 4 mg/kg is recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia and thrombocytopenia

8.1.3 General considerations for IV administration

Actemra concentrate for intravenous infusion should be diluted to 100 ml by a healthcare professional using aseptic technique.

- From a 100 ml infusion bag, withdraw a volume of 0.9% (9 mg/ml) sterile, non-pyrogenic sodium chloride solution for injection equal to the volume of Actemra concentrate required for the patient's dose, under aseptic conditions. The expiry date should always be checked before use
- Slowly add Actemra concentrate for IV infusion from each vial into the infusion bag. To mix the solution, gently invert the bag to avoid foaming
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted
- The fully diluted Actemra solution for infusion may be stored at 2°C–8°C or room temperature (if diluted under controlled and validated aseptic conditions) for up to 24 hours and should be protected from light. Actemra solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used
- Allow the fully diluted Actemra solution to reach room temperature prior to infusion
- The infusion should be administered over 60 minutes, and must be administered with an infusion set. Do not administer as an IV push or bolus
- Actemra should not be infused concomitantly in the same IV line with other medications. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of Actemra with other medications

For further information, please consult the Step-by-Step Dosing and Administration Guide for Actemra.

8.2 pJIA

For additional patient dosage and administration information, refer to the *STEP-BY-STEP DOSING AND ADMINISTRATION GUIDE*

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of pJIA. All patients treated with Actemra should be given the Patient Alert Card.

Suitability of the patient or parent/guardian for subcutaneous home use should be assessed and parent/guardian instructed to inform a healthcare professional before administering the next dose if they experience symptoms of an allergic reaction. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions (see earlier section). Self-administration is not recommended in children with pJIA. Administration should be done by a health care professional or parent/guardian/caregiver.

8.2.1 Actemra IV in pJIA

The recommended dosing in patients above 2 years of age is 8 mg/kg once every 4 weeks in patients weighing greater than or equal to 30 kg or 10 mg/kg once every 4 weeks in patients weighing less than 30 kg. The dose should be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time.

The safety and efficacy of intravenous Actemra in children below 2 years of age has not been established. No data are available.

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

Reduction of Actemra dose due to laboratory abnormalities has not been studied in pJIA patients. Actemra IV in pJIA dosing based on laboratory abnormalities is discussed in further detail earlier this document in Laboratory Parameters section

Available data suggest that clinical improvement is observed within 12 weeks of initiation of treatment with Actemra. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe.

8.2.1.1 Method of administration of Actemra IV in pJIA

Method of administration of Actemra IV in pJIA*		
After dilution, Actemra for RA, sJIA and pJIA patients should be administered as an intravenous infusion over 1 hour		
Weight of the patient with pJIA	pJIA patients ≥ 30 kg	pJIA patients < 30 kg
Actemra Dilution	Actemra should be diluted to a final volume of 100 ml with sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection using aseptic technique.	Actemra should be diluted to a final volume of 50 ml with sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection using aseptic technique.
Instructions on dilution of Actemra before administration.	Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection from a 100 ml infusion bag, equal to the volume of Actemra concentrate required for the patients dose, under aseptic conditions. The required amount of Actemra concentrate (0.4 ml/kg) should be withdrawn from the vial and placed in the 100 ml infusion bag. This should be a final volume of 100 ml. To mix the solution, gently invert the infusion bag to avoid foaming	Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution for injection from a 50 ml infusion bag, equal to the volume of Actemra concentrate required for the patients dose, under aseptic conditions. The required amount of Actemra concentrate (0.6 ml/kg) should be withdrawn from the vial and placed in the 50 ml infusion bag. This should be a final volume of 50 ml. To mix the solution, gently invert the infusion bag to avoid foaming.
* Note: Actemra subcutaneous formulation is not intended for intravenous administration.		

8.2.2 General considerations for IV administration

- Expiry date should always be checked before use
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted
- The fully diluted Actemra solution for infusion may be stored at 2°C–8°C or room temperature (if diluted under controlled and validated aseptic conditions) for up to 24 hours and should be protected from light. Actemra solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used
- Allow the fully diluted Actemra solution to reach room temperature prior to infusion
- The infusion should be administered over 60 minutes, and must be administered with an infusion set. Do not administer as an IV push or bolus

- Actemra should not be infused concomitantly in the same IV line with other medications. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of Actemra with other medications

For further information, please consult the *Step-by-Step Dosing and Administration Guide* for Actemra

8.3 SJIA

8.3.1 Actemra IV in sJIA

The recommended dose of IV Actemra in sJIA patients is 8 mg/kg once every 2 weeks in patients weighing ≥30 kg, or 12 mg/kg once every 2 weeks in patients weighing <30 kg. The dose should be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time.

- Actemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX
- There is no experience of the use of Actemra with TNF antagonists or other biological treatments for sJIA patients. Actemra is not recommended for use with other biological agents

8.3.2 General dose advice

- Dose interruptions of Actemra for laboratory abnormalities are recommended
- Reduction of Actemra dose due to laboratory abnormalities has not been studied in sJIA
- If appropriate, the dose of concomitant MTX and/or other medications should be modified or dosing stopped and Actemra dosing interrupted until the clinical situation has been evaluated
- The decision to discontinue Actemra for a laboratory abnormality should be based on the medical assessment of the individual patient

8.3.3 General considerations for administration

Actemra concentrate for intravenous (IV) infusion should be diluted by a healthcare professional using aseptic technique.

For patients <30 kg	For patients ≥30 kg
• From a **50 ml** infusion bag, withdraw a volume of 0.9% (9 mg/ml) sterile, non-pyrogenic sodium chloride solution for injection equal to the volume of Actemra concentrate required for the patient's dose	• From a **100 ml** infusion bag, withdraw a volume of 0.9% (9 mg/ml) sterile, non-pyrogenic sodium chloride solution for injection equal to the volume of Actemra concentrate required for the patient's dose
• The required amount of Actemra concentrate (**0.6 ml/kg**) should be withdrawn from the vial and placed in the 50 ml infusion bag. This should be a final volume of 50 ml	• The required amount of Actemra concentrate (**0.4 ml/kg**) should be withdrawn from the vial and placed in the 100 ml infusion bag. This should be a final volume of 100 ml

- Slowly add Actemra concentrate for IV infusion from each vial into the infusion bag. To mix the solution, gently invert the bag to avoid foaming
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted
- The fully diluted Actemra solutions for infusion may be stored at 2–8°C or room temperature (if diluted under controlled and validated aseptic conditions) for up to 24 hours and should be protected from light. Actemra solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used
- Allow the fully diluted Actemra solution to reach room temperature prior to infusion
- The infusion should be administered over 60 minutes and must be administered with an infusion set. Do not administer as an IV push or bolus
- Actemra should not be infused concomitantly in the same IV line with other drugs. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of Actemra with other medications

9. Actemra® (tocilizumab) Important Safety Information

9.1 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Active, severe infections.

9.2 Special warnings and precautions for use

9.2.1 Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including Actemra. Actemra treatment should not be initiated in patients with active infections. Administration of Actemra should be interrupted if a patient develops a serious infection until the infection is controlled. Healthcare professionals should exercise caution when considering the use of Actemra in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes, or interstitial lung disease) which may predispose patients to infections.

Vigilance for the timely detection of serious infection is recommended for patients receiving immunosuppressive agents such as Actemra, as signs and symptoms of acute inflammation may be lessened, associated with suppression of the acute phase reactants. The effects of Actemra on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients (including younger children who may be less able to communicate their symptoms) and parents/guardians of paediatric patients should be instructed to contact their healthcare professional immediately if any symptoms suggesting infection appear, in order to ensure rapid evaluation and appropriate treatment.

9.2.1.1 Tuberculosis

As recommended for other biological therapies, all 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. Prescribers 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, or parents/guardians of pediatric patients should be advised to **seek medical advice** if signs/symptoms (e.g. persistent cough, wasting/weight loss, low grade fever) suggestive of a TB infection occur during or after therapy with Actemra.

9.2.1.2 Viral reactivation

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

9.2.1.3 Complications of diverticulitis

Events of diverticular perforations as complications of diverticulitis have been reported uncommonly in patients treated with Actemra. Actemra should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage and/or

unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis, which can be associated with gastrointestinal perforation.

9.2.2 Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported in association with Actemra. Such reactions may be more severe, and potentially fatal, in patients who have experienced hypersensitivity reactions during previous treatment with Actemra even if they have received premedication with steroids and antihistamines. Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during treatment with Actemra IV. If an anaphylactic reaction or other serious hypersensitivity reaction occurs, administration of Actemra should be stopped immediately, appropriate therapy initiated and Actemra should be permanently discontinued. Fatal anaphylaxis has been reported after marketing authorisation during treatment with intravenous Actemra.

9.2.3 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.

9.2.3.1 Hepatic transaminase elevations

In clinical trials, transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with Actemra treatment, without progression to hepatic injury. An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with Actemra. When clinically indicated, other liver function tests including bilirubin should be considered.

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 is not recommended.

In RA and patients, 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 ALT or AST elevations > 3 to 5 x ULN, Actemra treatment should be interrupted.

In pJIA and sJIA patients, ALT and AST should be monitored at the time of the second administration and thereafter according to good clinical practice.

Please see sections 4.2 Posology and Method of Administration and 4.8 Undesirable Effects of the SmPc for further information.

9.2.4 Haematological abnormalities

Decreases in neutrophil and platelet counts have occurred following treatment with Actemra IV or Actemra SC in combination with MTX. 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 below 100 x 10^3/ µL). In patients who develop an ANC < 0.5 x 10^9/ L or a platelet count < 50 x 10^3/µL, continued treatment is not recommended.

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

In RA and patients, neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice.

In pJIA and sJIA patients, neutrophils and platelets should be monitored at the time of the second administration and thereafter according to good clinical practice.

9.2.5 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. 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 4 to 8 weeks following initiation of Actemra therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

9.2.6 Neurological 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.

9.2.7 Malignancy

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

9.2.8 Vaccinations

Live and live attenuated vaccines should not be given concurrently with Actemra as clinical safety has not been established. It is recommended that all patients, particularly paediatric or elderly patients, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Actemra therapy. The interval between live vaccinations and initiation of Actemra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

9.2.9 Cardiovascular risk

The risk of cardiovascular disorders is increased in patients with RA. Patients receiving Actemra should have their risk factors (e.g. hypertension, hyperlipidaemia) managed as part of usual standard of care.

9.2.10 Combination with TNF antagonists

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

9.2.11 Macrophage activation syndrome (MAS)

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

9.2.12 Sodium

Actemra IV contains 1.17 mmol (or 26.55 mg) 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 this medicinal product contain less than 1 mmol sodium (23 mg), i.e. essentially 'sodium free'.

9.2.13 Product traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

9.3 Fertility, pregnancy and lactation

9.3.1 Women of childbearing potential

Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

9.3.2 Pregnancy

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

Actemra should not be used during pregnancy unless clearly necessary.

9.3.3 Breast-feeding

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

9.3.4 Fertility

Available non-clinical Actemra data do not suggest an effect on fertility.

9.4 Undesirable effects

9.4.1 Summary of the safety profile

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

In RA patients, the most serious ADRs were serious infections, complications of diverticulitis, and hypersensitivity reactions.

The safety observed for Actemra SC in RA and was consistent with the known safety profile of Actemra IV with a higher frequency of injection site reactions observed with Actemra SC.

In pJIA patients, the most common adverse drug reactions were similar in type to those seen in Rheumatoid Arthritis (RA) patients, in general. The types of ADRs in pJIA patients were similar to those seen in RA and sJIA patients. When compared to the adult RA population, events of nasopharyngitis, headache, nausea, and decreased neutrophil count were more frequently reported in the pJIA population. Events of cholesterol increased were less frequently reported in the pJIA population than in the adult RA population.

9.4.2 Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

For full information on all possible adverse events please see the Summary of Product Characteristics (SmPC) or the Patient Leaflet, which can be found at the website of Scientific Centre of Drug and Medical Technology Expertise after Academician Emil Gabrielyan" JSC via following adress: www.pharm.am .

Call for reporting

Consult the PIL/SmPC before prescribing, preparing or administering Actemra

For full information on all possible adverse events please see the Summary of Product Characteristics (SmPC) or the Patient Leaflet, which can be found at the at the website of Scientific Centre of Drug and Medical Technology Expertise after Academician Emil Gabrielyan" JSC via following adress: www.pharm.am .

Adverse reactions should also be reported to Roche Medical Information via the Company contact point, that is provided below:

Drug Safety Department of Roche Moscow via contacts as follows: email: moscow.ds@roche.com, mobile phone: +7-495-229 2999, fax: +7-495- 229 7999 or try website: www.roche.ru.

Company contact point:
Local Safety Responsible for Roche products in Armenia, Gayane Ghazaryan, via following contac
+37491796688, email address: gayaneh.ghazaryan@gmail.com or Rima Davtyan tel: +01073464
email address: rima@pharmatech.am .

This educational material is mandatory as a condition of the marketing authorisation of Actemra in order to further minimise important selected risks.

Vahan Arushanyan
General Director, PharmaTech CJSC

27.11.18 _____
date signature

Gayane Ghazaryan , Safety Responsible
for Roche products in Armenia, PharmaTech CJSC

26.11.18 _____
date / signature