Actemra for Rheumatoid Arthritis

IMPORTANT EFFICACY AND SAFETY INFORMATION

To assist healthcare professionals in assessing the benefits and risks associated with Actemra therapy in patients with rheumatoid arthritis

This educational material is mandatory as a condition of the marketing authorisation ofActemra 20mg/ml; (1) glass vial 10ml and 20mg/ml; (1) glass vial 4mlconcentrate for solution for i/v infusion in the treatment of adult patients with moderate to severe active rheumatoid arthritis

Indications and usage

Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients. Actemra can be used alone or in combination with methotrexate (MTX) and/or other disease modifying anti-rheumatic drugs (DMARDs). Actemra has been shown to inhibit progression of joint damage as measured by X-ray and to improve physical function.

Patient counselling information and laboratory monitoring

Patient counselling information

Patients should be advised of the potential risks and benefits of Actemra.

The risks associated with Actemra treatment include

- Infections:
  Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including Actemra. Inform patients that Actemra may lower their resistance to infections.

  Instruct the patient 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

- Hypersensitivity reactions:
  Inform the patient that serious allergic reactions including anaphylaxis have been reported in association with Actemra. 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 after marketing authorisation during treatment with intravenous Actemra.

  Instruct the patient 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

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

• Gastrointestinal side effects:
Inform patients that some patients who have been treated with Actemra have had serious side effects in the stomach and intestines. **Instruct the patient 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 patient 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
  - Are pregnant, might be pregnant, intend to become pregnant, or are breast-feeding
  - 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

Laboratory monitoring

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.

Clinical response

The potential benefits associated with Actemra treatment

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

Efficacy results from Study WA28119

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

* p<0.0001
** p<0.005 (threshold for significance for primary and key secondary tests of superiority)
***Descriptive p value ≤0.005
****Flare: recurrence of GCA signs or symptoms and/or ESR ≥30 mm/h – Increase in the prednisone dose required
Remission: absence of flare and normalization of the CRP
Sustained remission: remission from week 12 to week 52 –Patients must adhere to the protocol-defined prednisone taper
[1] analysis of the time (in days) between clinical remission and first disease flare
[2] p-values are determined using a Van Elteren analysis for non-parametric data
[§] statistical analyses has not been performed
N/A= Not applicable
HR = Hazard Ratio
CI = Confidence Interval

Warnings and precautions

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 biological treatments for moderate-to-severe RA 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 should be instructed to contact their healthcare professional immediately if any symptoms suggesting infection appear, in order to ensure rapid evaluation and appropriate treatment.

Tuberculosis

As recommended for other biologic therapies in RA, patients should be screened for latent 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 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.

Viral reactivation

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

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.

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. 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.

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.

Laboratory parameters

- **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	Actemra SC
	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	Interrupt Actemra dosing When ANC increases >1 x 10^9/l resume Actemra dosing every other week and increase to every week injection, as clinically appropriate
ANC <0.5	Discontinue Actemra	

• Platelets

Decreases in platelet counts have occurred following treatment with Actemra 8 mg/kg IV once every four weeks and Actemra 162 mg SC once a week 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

• 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.

- **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.

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.

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.

Malignancy

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

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 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.

Cardiovascular risk in RA patients

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.

Renal impairment

No dose adjustment is required in patients with mild or moderate renal impairment. Actemra has not been studied in patients with moderate-to-severe renal impairment. Renal function should be monitored closely in these patients.

Product traceability

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

Undesirable effects

Summary of the safety profile

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.

Actemra IV

- **Infections**

In the 6-month controlled 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 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 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.

Other adverse reactions

Summary of ADRs occurring in patients with RA receiving RoACTEMRA treatment as monotherapy or in combination with MTX or other DMARDs in the double-blind controlled period

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Infections and infestations	Upper respiratory tract infections	Cellulitis, Pneumonia, Oral herpes simplex, Herpes zoster	Diverticulitis
Gastrointestinal disorders		Abdominal pain, Mouth ulceration, Gastritis	Stomatitis, Gastric ulcer
Skin and subcutaneous tissue disorders		Rash, Pruritus, Urticaria	
Nervous system disorders		Headache, Dizziness	
Investigations		Hepatic transaminases increased, Weight increased, Total bilirubin increased*	
Vascular disorders		Hypertension	
Blood and lymphatic system disorders		Leukopaenia, Neutropaenia	
Metabolism and nutrition disorders	Hypercholesterolaemia*		Hypertriglyceridaemia
General disorders and administration site conditions		Peripheral oedema, Hypersensitivity reactions	
Eye disorders		Conjunctivitis	
Respiratory, thoracic and mediastinal disorders		Cough, Dyspnoea	
Renal disorders			Nephrolithiasis
Endocrine disorders			Hypothyroidism

* Includes elevations collected as part of routine laboratory monitoring

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

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.

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.

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.

Malignancies

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

Undesirable effects

Drug 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.

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

Interactions with CYP450 substrates

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 tocilizumab, patients taking medicinal products which are individually adjusted and are metabolised via CYP450 3A4, 1A2 or 2C9 (e.g. methylprednisolone, dexamethasone, (with the possibility for oral glucocorticoid withdrawal syndrome), 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 (t1/2), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

Use in specific populations

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.

Women of childbearing potential

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

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 woman.

Fertility

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

Older people

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

Renal impairment

No dose adjustment is required in patients with mild renal impairment. Actemra has not been studied in patients with moderate-to-severe renal impairment. Renal function should be closely monitored in these patients.

Hepatic impairment

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

Paediatric patients

The safety and efficacy of Actemra SC fixed-dose formulation in children from birth to less than 18 years have not been established. No data are available.

Dosage and administration

Actemra IV

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

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

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

Actemra® (tocilizumab) Important Safety Information

Therapeutic indications

Actemra, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients. Actemra can be used alone or in combination with methotrexate (MTX) and/or other diseasemodifying anti-rheumatic drugs (DMARDs). Actemra has been shown to inhibit progression of joint damage as measured by X-ray and to improve physical function:

In these patients, 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.

Actem

Contraindications

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

Special warnings and precautions for use

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 and 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 for moderate-to-severe RA 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 should be instructed to contact their healthcare professional immediately if any symptoms suggesting infection appear, in order to ensure rapid evaluation and appropriate treatment.

Tuberculosis

As recommended for other biological treatments in 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.

Decreases in neutrophil and platelet counts have occurred following treatment with Actemra 8 mg/kg IV 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 2×10^9/L. Caution should be exercised when considering initiation of Actemra treatment in patients with a low platelet count (i.e. platelet count below 100×10^3/ µL). In patients who develop an ANC < 0.5×10^9/ L or a platelet count < 50×10^3/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 , neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice.

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.

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.

Malignancy

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

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 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.

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.

Viral reactivation

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

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.

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. 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.

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.

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 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.

Haematological abnormalities

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.

Combination with TNF antagonists
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.

Sodium
This medicinal product 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'.

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

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 absolutely necessary.

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.

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

Undesirable effects

Summary of the safety profile
The most commonly reported adverse drug reactions (ADRs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

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

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 to «SCIENTIFIC CENTRE OF DRUG AND MEDICAL TECHNOLOGY EXPERTISE AFTER ACADEMICIAN E. GABRIELYAN» CJSC website (www.pharm.am) Pharmacovigilance department via email: vigilance@pharm.am or hotline telephone: (+374 10) 237265, (+374 98) 773368 .

You can also report side effects directly to PharmaTech Safety department via mobile phone: +37491796688, or email: gayaneh.ghazaryan@gmail.com or direct your report to Drug Safety Department of Roche Moscow via contacts below: email: moscow.ds@roche.com, mobile phone: +7-495-229 2999, fax: +7-495- 229 7999 or try website: www.roche.ru.

Product traceability

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

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 «SCIENTIFIC CENTRE OF DRUG AND MEDICAL TECHNOLOGY EXPERTISE AFTER ACADEMICIAN E. GABRIELYAN» CJSC website (www.pharm.am).

Vahan Arushanyan,
Director of PharmaTech CJSC

Signature:_____

Date: 27.03.18

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

Signature:_____

Date: 27.03.18