

# ACTEMRA

## Laboratory parameters

### Neutrophils

Decreases in neutrophil counts have occurred following treatment with ACTEMRA 8 mg/kg in combination with disease-modifying anti-rheumatic drugs (DMARDs).

Caution should be exercised when considering initiation of ACTEMRA treatment in patients with a low neutrophil count (ie, absolute neutrophil count (ANC)  $<2 \times 10^9/L$ ). In patients with an ANC  $<0.5 \times 10^9/L$ , treatment is not recommended.

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

### Low ANC

Lab value (cells $\times 10^9/L$ )	Action
ANC $>1$	Maintain dose
ANC 0.5 to 1	Interrupt ACTEMRA dosing When ANC increases above $1 \times 10^9/L$ , resume ACTEMRA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
ANC $<0.5$	Discontinue ACTEMRA

### Platelets

Decreases in platelet counts have occurred following treatment with ACTEMRA 8 mg/kg in combination with DMARDs.

Caution should be exercised when considering initiation of ACTEMRA treatment in patients with a low platelet count (ie, platelet count below  $100 \times 10^3/\mu L$ ). In patients with a platelet count  $<50 \times 10^3/\mu L$  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

Lab value (cells $\times 10^3/\mu L$ )	Action
50 to 100	Interrupt ACTEMRA dosing When platelet count increases above $100 \times 10^3/\mu L$ resume ACTEMRA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
$<50$	Discontinue ACTEMRA

### Hepatic transaminases

Caution should be exercised when considering initiation of ACTEMRA treatment in patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST)  $> 1.5 \times$  upper limit of normal (ULN). In patients with baseline ALT or AST  $> 5 \times$  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  $> 3-5 \times$  ULN, confirmed by repeat testing, ACTEMRA treatment should be interrupted. Once the patient's hepatic transaminases are below  $3 \times$  ULN, treatment with ACTEMRA may recommence at 4 or 8 mg/kg.

### Liver enzyme abnormalities

Lab value	Action
$>1$ to $3 \times$ ULN	Dose modify concomitant methotrexate if appropriate For persistent increases in this range, reduce dose of ACTEMRA 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 $5 \times$ ULN Confirmed by repeat testing	Interrupt ACTEMRA dosing until $<3 \times$ ULN When values reach $<3 \times$ ULN, resume ACTEMRA at 4 mg/kg or 8 mg/kg For persistent increases $>3 \times$ ULN, discontinue ACTEMRA
$>5 \times$ ULN	Discontinue ACTEMRA

 **ACTEMRA**<sup>®</sup>  
tocilizumab

### ACTEMRA

#### 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 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.

##### Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Active, severe infections.

##### Infections

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 (eg, diverticulitis, diabetes) 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 when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

##### Tuberculosis

As recommended for other biological treatments in RA, 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.

##### 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 have been reported in association with infusion of ACTEMRA in approximately 0.3% of patients. Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during administration of 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, as the safety of ACTEMRA in these patients has not been adequately studied.

##### 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 (eg, MTX) were used in combination with ACTEMRA.

Caution should be exercised when considering initiation of ACTEMRA treatment in patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST)  $> 1.5 \times$  upper limit of normal (ULN). In patients with baseline ALT or AST  $> 5 \times$  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  $> 3-5 \times$  ULN, confirmed by repeat testing, ACTEMRA treatment should be interrupted. Once the patient's hepatic transaminases are below  $3 \times$  ULN, treatment with ACTEMRA may recommence at 4 or 8 mg/kg.

##### 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.

Caution should be exercised when considering initiation of ACTEMRA treatment in patients with a low neutrophil or platelet count (ie, absolute neutrophil count (ANC)  $< 2 \times 10^9/L$  or platelet count below  $100 \times 10^3/\mu L$ ). In patients with an ANC  $< 0.5 \times 10^9/L$  or a platelet count  $< 50 \times 10^3/\mu L$  treatment is not recommended.

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.

##### Cardiovascular risk

RA patients have an increased risk for cardiovascular disorders and should have risk factors (eg, 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), ie, essentially 'sodium free'.

##### Undesirable effects

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