IMPORTANT EFFICACY AND SAFETY INFORMATION

to assist healthcare professionals in assessing the benefits and risks associated with RoACTEMRA therapy

RoACTEMRA®
tocilizumab

Roche

Indications and Usage

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

RoACTEMRA 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 methotrexate.

In the Phase III development programme, the efficacy of RoACTEMRA in alleviating the signs and symptoms of RA was assessed in 5 randomised, double-blind, multi-centre studies. Studies I-V enrolled patients ≥18 years of age with active RA diagnosed according to the American College of Rheumatology (ACR) criteria and who had at least 8 tender and 6 swollen joints at baseline. Study II examined the efficacy of RoACTEMRA on the rate of progression of joint damage and improvement of physical function in RA patients.

Patient Counselling Information and Laboratory Monitoring

Patient counselling information

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

- Infections:

Inform patients that RoACTEMRA may lower their resistance to infections. Instruct the patient of the importance of contacting their doctor immediately when symptoms suggesting infection appear in order to assure rapid evaluation and appropriate treatment.

- Gastrointestinal side effects:

Inform patients that some patients who have been treated with RoACTEMRA have had serious side effects in the stomach and intestines. Instruct the patient about the importance of contacting their doctor immediately when symptoms of severe, persistent abdominal pain, haemmorhage and/or unexplained change in bowel habits with fever appear, to assure rapid evaluation and appropriate treatment.

- Hypersensitivity reactions:

Inform patients about potential hypersensitivity reactions. Most reactions happen during infusion or within 24 hours after infusion. They can range from mild to severe.

— Mild to moderate reactions include:

- Hypertension
- Headache
- Skin reactions, such as rash, pruritus and urticaria

- Severe reactions include:

—Anaphylaxis

- Before you administer RoACTEMRA, 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

—Are pregnant or want 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

—Are taking other biological drugs to treat RA, as well as atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin or benzodiazepines

—Have had or now have viral hepatitis or any another hepatic disease

—Have a history of gastrointestinal ulcers or diverticulitis

—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

Laboratory monitoring

Alanine aminotransferase (ALT) and 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. Neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. Lipids should be monitored 4 to 8 weeks following initiation of RoACTEMRA therapy.

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Clinical Response

The percentages of patients achieving ACR20, ACR50 and ACR70 are shown below. In all studies, patients treated with 8 mg/kg RoACTEMRA 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 RoACTEMRA 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	
Wk	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 - DMARD
*$p<0.05$, Tocilizumab vs. Placebo + MTX / DMARDs
**$p<0.01$, Tocilizumab vs. Placebo + MTX / DMARDs
***$p<0.0001$, Tocilizumab vs. Placebo + MTX / DMARDs

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 RoACTEMRA-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 RoACTEMRA (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 to 48% at 52 weeks and 33% of patients at Week 24.

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RoACTEMRA® tocilizumab

Warnings and Precautions

Infections
RoACTEMRA treatment should not be initiated in patients with active infections. Administration of RoACTEMRA 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 RoACTEMRA in patients with a history of recurring infection 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 RoACTEMRA on C-reactive protein, 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 biologic therapies in RA, patients should be screened for latent TB infection prior to starting RoACTEMRA therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating RoACTEMRA.

Viral reactivation
Viral reactivation (eg, hepatitis B virus) has been reported with biologic therapies for rheumatoid arthritis. In clinical studies with tocilizumab, patients who screened positive for hepatitis were excluded.

Complications of diverticulitis
Events of diverticular perforations as complications of diverticulitis have been reported uncommonly with RoACTEMRA. RoACTEMRA 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.

Neurological disorders
Physicians should be vigilant for symptoms potentially indicative of new-onset central demyelinating disorders. The potential for central demyelination with RoACTEMRA is currently unknown.

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

Hypersensitivity reactions
Serious hypersensitivity reactions have been reported in association with infusion of RoACTEMRA in approximately 0.3% of patients. Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during administration of RoACTEMRA.

Cardiovascular risk in RA patients
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.

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

Active hepatic disease and hepatic impairment
Treatment with RoACTEMRA, 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.

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

Laboratory parameters
- Neutrophils

Decreases in neutrophil counts have occurred following treatment with RoACTEMRA 8 mg/kg in combination with DMARDs.

Caution should be exercised when considering initiation of RoACTEMRA treatment in patients with a low neutrophil count (ie, absolute neutrophil count <2 x 10^9/L). In patients with an absolute neutrophil count <0.5 x 10^9/L 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 RoACTEMRA to date.

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

Low absolute neutrophil count (ANC)

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

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Warnings and Precautions (continued)

- Platelets

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

Caution should be exercised when considering initiation of RoACTEMRA treatment in patients with a low platelet count (ie, platelet count below 100 x 10^3/μL). In patients with a platelet count <50 x 10^3/μL 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 x 10^3/μL)	Action
50 to 100	Interrupt RoACTEMRA dosing When platelet count increases above 100 x 10^3/μL resume RoACTEMRA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
<50	Discontinue RoACTEMRA

Laboratory parameters

- Hepatic transaminases

In clinical trials, transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with RoACTEMRA treatment, without progression to hepatic injury. An increased frequency of these elevations was observed when potential hepatotoxic drugs (eg, MTX) were used in combination with RoACTEMRA.

Caution should be exercised when considering initiation of RoACTEMRA treatment in patients with elevated ALT or 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 > 3–5 x ULN, confirmed by repeat testing, RoACTEMRA treatment should be interrupted.

Liver enzyme abnormalities

Lab value	Action
>1 to 3 x ULN	Dose modify concomitant MTX if appropriate For persistent increases in this range, reduce dose of RoACTEMRA to 4 mg/kg or interrupt RoACTEMRA until ALT or AST have normalised Restart with 4 mg/kg or 8 mg/kg as clinically appropriate
>3 to 5 x ULN Confirmed by repeat testing	Interrupt RoACTEMRA dosing until <3 x ULN and follow recommendations above for >1 to 3 x ULN For persistent increases >3 x ULN, discontinue RoACTEMRA
>5 x ULN	Discontinue RoACTEMRA

- Lipids

Elevations in lipid parameters including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were observed in patients treated with RoACTEMRA. 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 RoACTEMRA therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

Undesirable Effects

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

- Infections

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

In 6-month controlled clinical studies, the rate of serious infections with RoACTEMRA 8 mg/kg plus DMARDs was 5.3 events per 100 patient-years exposure compared to 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 RoACTEMRA group and 1.5 events per 100 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.

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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	
Metabolic 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

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 RoACTEMRA 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 3778 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 RoACTEMRA and requiring treatment discontinuation were reported in a total of 13 out of 3778 patients (0.3%) treated with RoACTEMRA during the controlled and open-label clinical studies. These reactions were generally observed during the second to fifth infusions of RoACTEMRA.

Immunogenicity

A total of 2876 patients have been tested for anti-tocilizumab antibodies in the 6-month controlled clinical trials. Of the 46 patients (1.6%) who developed anti-tocilizumab 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 clinical data are insufficient to assess the potential incidence of malignancy following exposure to RoACTEMRA. Long-term safety evaluations are ongoing.

Drug Interactions

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

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

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Drug Interactions (continued)

Interactions with CYP450 substrates

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

In vitro studies with cultured human hepatocytes demonstrated that IL-6 caused a reduction in CYP1A2, CYP2C9, CYP2C19 and CYP3A4 enzyme expression. RoACTEMRA 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 RoACTEMRA, to the level similar to, or slightly higher than, those observed in healthy subjects.

When starting or stopping therapy with RoACTEMRA, patients taking medicinal products which are individually adjusted and are metabolised via CYP450, 3A4, 1A2 or 2C9 (eg, atorvastatin, calcium channel blockers, theophylline, warfarin, 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 RoACTEMRA 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 RoACTEMRA 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. Women of childbearing potential must use effective contraception during (and up to 3 months after) treatment.

RoACTEMRA should not be used during pregnancy unless clearly necessary.

Lactation

It is unknown whether RoACTEMRA is excreted in human breast milk. The excretion of RoACTEMRA in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with RoACTEMRA should be made taking into account the benefit of breast-feeding to the child and the benefit of RoACTEMRA therapy to the woman.

Paediatric patients

RoACTEMRA is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy.

Elderly patients

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. RoACTEMRA has not been studied in patients with moderate to severe renal impairment. Renal function should be closely monitored in these patients.

Hepatic impairment

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

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Dosage and Administration

The recommended dose of RoACTEMRA 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 intravenous (IV) infusion.

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

General dose advice

- It is recommended that RoACTEMRA not be initiated in patients with an ANC below 0.5 x 10^9/L, platelet count below 50,000/µL, or who have ALT or AST above 3 times the ULN
- 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, neutropaenia and thrombocytopaenia

General considerations for administration

RoACTEMRA concentrate for intravenous infusion should be diluted to 100 mL by a healthcare professional using aseptic technique as follows:

- From a 100-mL infusion bag, withdraw a volume of 0.9% (9 mg/mL) sodium chloride injection equal to the volume of RoACTEMRA solution required for the patient's dose
- Slowly add RoACTEMRA concentrate for IV infusion from each vial into the infusion bag. To mix the solution, gently invert the bag to avoid foaming
- Parenteral drug 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 RoACTEMRA solutions 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. RoACTEMRA solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used
- Allow the fully diluted RoACTEMRA solution to reach room temperature prior to infusion
- The infusion should be administered over 1 hour, and must be administered with an infusion set. Do not administer as an intravenous push or bolus
- RoACTEMRA 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 RoACTEMRA with other drugs

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RoACTEMRA® (tocilizumab) Important Safety Information

Therapeutic indications
RoACTEMRA, 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, RoACTEMRA can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

RoACTEMRA 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 methotrexate.

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

Infections
RoACTEMRA treatment should not be initiated in patients with active infections. Administration of RoACTEMRA 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 RoACTEMRA 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 RoACTEMRA 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 RoACTEMRA therapy. Patients with latent TB should be treated with standard anti-mycobacterial therapy before initiating RoACTEMRA.

Viral reactivation
Viral reactivation (eg, hepatitis B virus) has been reported with biologic therapies for rheumatoid arthritis. In clinical studies with tocilizumab, patients who screened positive for hepatitis were excluded.

Complications of diverticulitis
Events of diverticular perforations as complications of diverticulitis have been reported uncommonly with RoACTEMRA. RoACTEMRA 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 RoACTEMRA in approximately 0.3% of patients. Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during administration of RoACTEMRA.

Active hepatic disease and hepatic impairment
Treatment with RoACTEMRA, 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 RoACTEMRA 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 RoACTEMRA.

Caution should be exercised when considering initiation of RoACTEMRA 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 >3-5 x ULN, confirmed by repeat testing, RoACTEMRA treatment should be interrupted.

Haematological abnormalities
Decreases in neutrophil and platelet counts have occurred following treatment with RoACTEMRA 8 mg/kg in combination with MTX. There may be an increased risk of neutropaenia in patients who have previously been treated with a TNF antagonist.

Caution should be exercised when considering initiation of RoACTEMRA treatment in patients with a low neutrophil or platelet count (ie, absolute neutrophil count (ANC) $<2 \times 10^9$/L or platelet count below 100×10^3/µL). In patients with an ANC $<0.5 \times 10^9$/L or a platelet count $<50 \times 10^3$/µL 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 RoACTEMRA to date.

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 RoACTEMRA. 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 RoACTEMRA 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 RoACTEMRA 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 RoACTEMRA 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 RoACTEMRA with TNF antagonists or other biological treatments for RA. RoACTEMRA 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'.

Pregnancy
There are no adequate data from the use of RoACTEMRA 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. Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

RoACTEMRA should not be used during pregnancy unless clearly necessary.

Lactation
It is unknown whether RoACTEMRA is excreted in human breast milk. The excretion of RoACTEMRA in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with RoACTEMRA should be made taking into account the benefit of breast-feeding to the child and the benefit of RoACTEMRA therapy to the woman.

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

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