

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

RoACTEMRA 20 mg/ml concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml concentrate contains 20 mg tocilizumab*.

Each vial contains 80 mg of tocilizumab* in 4 ml (20 mg/ml).
 Each vial contains 200 mg of tocilizumab* in 10 ml (20 mg/ml).
 Each vial contains 400 mg of tocilizumab* in 20 ml (20 mg/ml).

*humanised IgG1 monoclonal antibody against the human interleukin-6 (IL-6) receptor produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipients

Each 80 mg vial contains 0.10 mmol (2.21 mg) sodium.
 Each 200 mg vial contains 0.20 mmol (4.43 mg) sodium.
 Each 400 mg vial contains 0.39 mmol (8.85 mg) sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to opalescent, colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 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.

4.2 Posology and method of administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA. Patients treated with RoACTEMRA should be given the Patient Alert Card.

Posology

The recommended posology is 8 mg/kg body weight, given once every 4 weeks.

For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended (see section 5.2).

Doses above 1.2 g have not been evaluated in clinical studies (see section 5.1).

Dose adjustments due to laboratory abnormalities (see section 4.4).

- Liver enzyme abnormalities

| Laboratory Value | Action |
|--|--|
| > 1 to 3 x Upper Limit of Normal (ULN) | Dose modify concomitant MTX if appropriate For persistent increases in this range, reduce RoACTEMRA dose to 4 mg/kg or interrupt RoACTEMRA until alanine aminotransferase (ALT) or aspartate aminotransferase (AST) have normalised Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate |
| > 3 to 5 x ULN (confirmed by repeat testing, see section 4.4). | 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 |

- Low absolute neutrophil count (ANC)

| Laboratory Value (cells x 10 ⁹ /l) | Action |
|---|---|
| ANC > 1 | Maintain dose |
| ANC 0.5 to 1 | Interrupt RoACTEMRA dosing When ANC increases > 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 |

- Low platelet count

| Laboratory Value (cells x 10 ⁹ /µl) | Action |
|--|---|
| 50 to 100 | Interrupt RoACTEMRA dosing When platelet count > 100 x 10 ⁹ /µl resume RoACTEMRA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate |
| < 50 | Discontinue RoACTEMRA |

Special populations

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 (see section 5.2). Renal function should be monitored closely in these patients.

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

Method of administration

After dilution, RoACTEMRA should be administered as an intravenous infusion over 1 hour.

RoACTEMRA 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.

For further information on dilution prior to administration, see section 6.6.

4.3 Contraindications

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

Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

Infections

RoACTEMRA treatment should not be initiated in patients with active infections (see section 4.3). Administration of RoACTEMRA should be interrupted if a patient develops a serious infection until the infection is controlled (see section 4.8). 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 (e.g. 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 tocilizumab 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 (e.g. 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 (see section 4.8). 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 (see section

4.8). 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 (see sections 4.2 and 4.8).

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 (see section 4.8). An increased frequency of these elevations was observed when potentially hepatotoxic drugs (e.g. 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 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 recommended modifications based on transaminases see section 4.2. 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 tocilizumab 8 mg/kg in combination with MTX (see section 4.8). 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 RoACTEMRA treatment in patients with a low neutrophil or platelet count (i.e. ANC < 2 x 10⁹/l or platelet count below 100 x 10⁹/µl). In patients with an ANC < 0.5 x 10⁹/l or a platelet count < 50 x 10⁹/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. For recommended dose modifications based on ANC and platelet counts, see section 4.2.

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 tocilizumab (see section 4.8). 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 (e.g. 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), i.e. essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

Population pharmacokinetic analyses did not detect any effect of MTX, non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids on tocilizumab clearance.

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 tocilizumab, is introduced.

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

In a study in RA patients, levels of simvastatin (CYP3A4) were decreased by 57% 1 week following a single dose of tocilizumab, 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. 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 tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of tocilizumab in pregnant women. A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose (see section 5.3). 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 tocilizumab is excreted in human breast milk. The excretion of tocilizumab 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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, given that dizziness has been commonly reported, patients who experience this adverse reaction should be advised not to drive or use machines until it has resolved.

4.8 Undesirable effects

The safety of tocilizumab has been studied in four placebo-controlled studies (studies II, III, IV and V), one MTX-controlled study (study I) and their extension periods (see section 5.1).

The double-blind controlled period was 6 months in four studies (studies I, III, IV and V) and was up to 2 years in one study (study II). In the double-blind controlled studies, 774 patients received tocilizumab 4 mg/kg in combination with MTX, 1,870 patients received tocilizumab 8 mg/kg in combination with MTX or other DMARDs and 288 patients received tocilizumab 8 mg/kg monotherapy.

The long-term exposure population includes all patients who received at least one dose of tocilizumab either in the double-blind control period or open-label extension phase in the studies. Of the 4,009 patients in this population, 3,577 received treatment for at least 6 months, 3,296 for at least 1 year, 2,806 received treatment for at least 2 years and 1,222 for 3 years.

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

The ADRs listed in Table 1 are presented by system organ class and frequency categories, defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10) or uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. Summary of ADRs occurring in patients with RA receiving tocilizumab as monotherapy or in combination with MTX or other DMARDs in the double-blind controlled period

| System Organ Class | Very Common | Common | Uncommon |
|--|------------------------------------|---|---------------------------|
| 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 | | Leukopenia, Neutropenia | |
| 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 |

Infections

In the 6-month controlled studies the rate of all infections reported with tocilizumab 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 tocilizumab 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 tocilizumab 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.

Gastrointestinal Perforation

During the 6-month controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient years with tocilizumab therapy. In the long-term exposure population the overall rate of gastrointestinal perforation was 0.28 events per 100 patient years. Reports of gastrointestinal perforation on tocilizumab were primarily reported as complications of diverticulitis including generalised purulent peritonitis, lower gastrointestinal perforation, fistulae and abscess.

Infusion reactions

In the 6-month controlled trials adverse events associated with infusion (selected events occurring during or within 24 hours of infusion) were reported by 6.9% of patients in the tocilizumab 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 6/3,778 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 tocilizumab and requiring treatment discontinuation were reported in a total of 13 out of 3,778 patients (0.3%) treated with tocilizumab during the controlled and open label clinical studies. These reactions were generally observed during the second to fifth infusions of tocilizumab (see section 4.4).

Immunogenicity

A total of 2,876 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, six had an associated medically significant hypersensitivity reaction, of which five led to permanent discontinuation of treatment. Thirty patients (1.1%) developed neutralising antibodies.

Haematological abnormalities:

Neutrophils

In the 6-month controlled trials decreases in neutrophil counts below $1 \times 10^9/l$ occurred in 3.4% of patients on tocilizumab 8 mg/kg plus DMARDs compared to < 0.1% of patients on placebo plus DMARDs. Approximately half of the patients who developed an ANC < $1 \times 10^9/l$ did so within 8 weeks after starting therapy. Decreases below $0.5 \times 10^9/l$ were reported in 0.3% patients receiving tocilizumab 8 mg/kg plus DMARDs. There was no clear association between decreases in neutrophils and the occurrence of serious infections.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 6-month controlled clinical trials.

Platelets

In the 6-month controlled trials decreases in platelet counts below $100 \times 10^3/\mu l$ occurred in 1.7% of patients on tocilizumab 8 mg/kg plus DMARDs compared to < 1% on placebo plus DMARDs. These decreases occurred without associated bleeding events.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 6-month controlled clinical trials.

Hepatic transaminase elevations

During the 6-month controlled trials transient elevations in ALT/AST > 3 x ULN were observed in 2.1% of patients on tocilizumab 8 mg/kg compared to 4.9% of patients on MTX and in 6.5% of patients who received 8 mg/kg tocilizumab plus DMARDs compared to 1.5% of patients on placebo plus DMARDs.

The addition of potentially hepatotoxic drugs (e.g. MTX) to tocilizumab monotherapy resulted in increased frequency of these elevations. Elevations of ALT/AST > 5 x ULN were observed in 0.7% of tocilizumab monotherapy patients and 1.4% of tocilizumab plus DMARD patients, the majority of whom were discontinued permanently from tocilizumab treatment. These elevations were not associated with clinically relevant increase in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic impairment. The incidence of indirect bilirubin greater than the upper limit of normal is 6.2% in patients treated with 8 mg/kg tocilizumab.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevation in ALT/AST remained consistent with what was seen in the 6-month controlled clinical trials.

Lipid parameters

During the 6-month controlled trials increases of lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol have been reported commonly. Approximately 24% of patients receiving RoACTEMRA in clinical trials experienced sustained elevations in total cholesterol $\geq 6.2 \text{ mmol/l}$, with 15% experiencing a sustained increase in LDL to $\geq 4.1 \text{ mmol/l}$. Elevations in lipid parameters responded to treatment with lipid-lowering agents.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevations in lipid parameters remained consistent with what was seen in the 6-month controlled trials.

Malignancies

The clinical data are insufficient to assess the potential incidence of malignancy following exposure to tocilizumab. Long-term safety evaluations are ongoing.

4.9 Overdose

There are limited data available on overdose with RoACTEMRA. One case of accidental overdose was reported in which a patient with multiple myeloma received a single dose of 40 mg/kg. No adverse reactions were observed.

No serious adverse reactions were observed in healthy volunteers who received a single dose up to 28 mg/kg, although dose limiting neutropenia was observed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors; ATC code: L04AC07.

Mechanism of action

Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis and neoplasia.

In clinical studies with tocilizumab, rapid decreases in CRP, erythrocyte sedimentation rate (ESR) and serum amyloid A (SAA) were observed.

Consistent with the effect on acute phase reactants, treatment with tocilizumab was associated with reduction in platelet count within the normal range. Increases in haemoglobin levels were observed, through tocilizumab decreasing the IL-6 driven effects on hepcidin production to increase iron availability. In tocilizumab-treated patients, decreases in the levels of CRP to within normal ranges were seen as early as Week 2, with decreases maintained while on treatment.

In healthy subjects administered tocilizumab in doses from 2 to 28 mg/kg, absolute neutrophil counts decreased to their lowest 3 to 5 days following administration. Thereafter, neutrophils recovered towards baseline in a dose-dependent manner. Rheumatoid arthritis patients demonstrated a similar pattern of absolute neutrophil counts following tocilizumab administration (see section 4.8).

Clinical efficacy

The efficacy of tocilizumab in alleviating the signs and symptoms of RA was assessed in five randomised, double-blind, multi-centre studies. Studies I-V enrolled patients \geq 18 years of age with active RA diagnosed according to the American College of Rheumatology (ACR) criteria and who had at least eight tender and six swollen joints at baseline.

In study I, tocilizumab was administered intravenously every 4 weeks as monotherapy. In studies II, III and V, tocilizumab was administered intravenously every 4 weeks in combination with MTX vs. placebo and MTX. In study IV, tocilizumab was administered intravenously every 4 weeks in combination with other DMARDs vs. placebo and other DMARDs. The primary endpoint for each of the five studies was the proportion of patients who achieved an ACR 20 response at Week 24.

Study I evaluated 673 patients who had not been treated with MTX within 6 months prior to randomisation and who had not discontinued previous MTX treatment as a result of clinically important toxic effects or lack of response. The majority (67%) of patients were MTX-naïve. Doses of 8 mg/kg of tocilizumab were given every 4 weeks as monotherapy. The comparator group was weekly MTX (dose titrated from 7.5 mg to a maximum of 20 mg weekly over an 8-week period).

Study II, a 2-year study with planned analyses at Week 24, Week 52 and Week 104, evaluated 1,196 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg of tocilizumab or placebo were given every 4 weeks as blinded therapy for 52 weeks in combination with stable MTX (10 mg to 25 mg weekly). After Week 52, all patients could receive open-label treatment with tocilizumab 8 mg/kg. Of the patients who completed the study who were originally randomised to placebo + MTX, 86% received open-label tocilizumab 8 mg/kg in Year 2. The primary endpoint at Week 24 was the proportion of patients who achieved an ACR 20 response. At Week 52 and Week 104 the co-primary endpoints were prevention of joint damage and improvement in physical function.

Study III evaluated 623 patients who had an inadequate clinical response to MTX. Doses of 4 or 8 mg/kg tocilizumab or placebo were given every 4 weeks, in combination with stable MTX (10 mg to 25 mg weekly).

Study IV evaluated 1,220 patients who had an inadequate response to their existing rheumatologic therapy, including one or more DMARDs. Doses of 8 mg/kg tocilizumab or placebo were given every 4 weeks in combination with stable DMARDs.

Study V evaluated 499 patients who had an inadequate clinical response or were intolerant to one or more TNF antagonist therapies. The TNF antagonist therapy was discontinued prior to randomisation. Doses of 4 or 8 mg/kg tocilizumab or placebo were given every 4 weeks in combination with stable MTX (10 mg to 25 mg weekly).

Clinical response

In all studies, patients treated with tocilizumab 8 mg/kg had statistically significant higher ACR 20, 50, 70 response rates at 6 months compared to control (Table 2). In study I, superiority of tocilizumab 8 mg/kg was demonstrated against the active comparator MTX.

The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race, number of prior treatments or disease status. Time to onset was rapid (as early as Week 2) and the magnitude of response continued to improve with duration of treatment. Continued durable responses were seen for over 3 years in the ongoing open label extension studies I-V.

In patients treated with tocilizumab 8 mg/kg, significant improvements were noted on all individual components of the ACR response including: tender and swollen joint counts; patient and physician global assessment; disability index scores; pain assessment and CRP compared to patients receiving placebo plus MTX or other DMARDs in all studies.

Patients in studies I-V had a mean Disease Activity Score (DAS28) of 6.5–6.8 at baseline. Significant reduction in DAS28 from baseline (mean improvement) of 3.1–3.4 were observed in tocilizumab-treated patients compared to control patients (1.3–2.1). The proportion of patients achieving a DAS28 clinical remission (DAS28 < 2.6) was significantly higher in patients receiving tocilizumab (28–34%) compared to 1–12% of control patients at 24 weeks. In study II, 65% of patients achieved a

DAS28 < 2.6 at Week 104 compared to 48% at 52 weeks and 33% of patients at Week 24.

In a pooled analysis of studies II, III and IV, the proportion of patients achieving an ACR 20, 50 and 70 response was significantly higher (59% vs. 50%, 37% vs. 27%, 18% vs. 11%, respectively) in the tocilizumab 8 mg/kg plus DMARD vs. the tocilizumab 4 mg/kg plus DMARD group ($p < 0.03$). Similarly the proportion of patients achieving a DAS28 remission (DAS28 < 2.6) was significantly higher (31% vs. 16% respectively) in patients receiving tocilizumab 8 mg/kg plus DMARD than in patients receiving tocilizumab 4 mg/kg plus DMARD ($p < 0.0001$).

Table 2. ACR responses in placebo-/MTX-/DMARDs-controlled studies (% patients)

| Week | Study I AMBITION | | Study II LITHE | | Study III OPTION | | Study IV TOWARD | | Study V RADIATE | |
|---------------|---------------------|------------|-----------------------------|--------------|-----------------------------|--------------|----------------------------------|----------------|-----------------------------|--------------|
| | TCZ 8 mg/ kg | MTX | TCZ 8 mg/ kg + MTX | PBO + MTX | TCZ 8 mg/ kg + MTX | PBO + MTX | TCZ 8 mg/ kg + DMARD | PBO + DMARD | TCZ 8 mg/ kg + MTX | PBO + 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
 PBO - Placebo
 DMARD - Disease modifying anti-rheumatic drug
 * - $p < 0.05$, TCZ vs. PBO + MTX/DMARD
 ** - $p < 0.01$, TCZ vs. PBO + MTX/DMARD
 *** - $p < 0.0001$, TCZ vs. PBO + MTX/DMARD

Major Clinical Response

After 2 years of treatment with tocilizumab plus MTX, 14% of patients achieved a major clinical response (maintenance of an ACR70 response for 24 weeks or more).

Radiographic response

In study II, in patients with an inadequate response to MTX, inhibition of structural joint damage was assessed radiographically and expressed as change in modified Sharp score and its components, the erosion score and joint space narrowing score. Inhibition of joint structural damage was shown with significantly less radiographic progression in patients receiving tocilizumab compared to control (Table 3).

In the open-label extension of study II the inhibition of progression of structural joint damage in tocilizumab plus MTX-treated patients was maintained in the second year of treatment. The mean change from baseline at Week 104 in total Sharp-Genant score was significantly lower for patients randomised to tocilizumab 8 mg/kg plus MTX ($p < 0.0001$) compared with patients who were randomised to placebo plus MTX.

Table 3. Radiographic mean changes over 52 weeks in study II

| | PBO + MTX (+ TCZ from Week 24) N = 393 | TCZ 8 mg/kg + MTX N = 398 |
|--------------------------|--|------------------------------|
| Total Sharp-Genant score | 1.13 | 0.29* |
| Erosion score | 0.71 | 0.17* |
| JSN score | 0.42 | 0.12** |

PBO - Placebo
 MTX - Methotrexate
 TCZ - Tocilizumab
 JSN - Joint space narrowing
 * - $p \leq 0.0001$, TCZ vs. PBO + MTX
 ** - $p < 0.005$, TCZ vs. PBO + MTX

Following 1 year of treatment with tocilizumab plus MTX, 85% of patients (n=348) had no progression of structural joint damage, as defined by a change in the Total Sharp Score of ≤ 0 , compared with 67% of placebo plus MTX-treated patients (n=290) ($p \leq 0.001$). This remained consistent following 2 years of treatment (83%; n=353). Ninety three percent (n=271) of patients had no progression between Week 52 and Week 104.

Health-related and quality of life outcomes

Tocilizumab-treated patients reported an improvement in all patient-reported outcomes (Health Assessment Questionnaire Disability Index - HAQ-DI), Short Form-36 and Functional Assessment of Chronic Illness Therapy questionnaires. Statistically significant improvements in HAQ-DI scores were observed in patients treated with RoACTEMRA compared with patients treated with DMARDs. During the open-label period of study II, the improvement in physical function has been maintained for up to 2 years. At Week 52, the mean change in HAQ-DI was -0.58 in the tocilizumab 8 mg/kg plus MTX group compared with

-0.39 in the placebo + MTX group. The mean change in HAQ-DI was maintained at Week 104 in the tocilizumab 8 mg/kg plus MTX group (-0.61).

Haemoglobin levels

Statistically significant improvements in haemoglobin levels were observed with tocilizumab compared with DMARDs ($p < 0.0001$) at Week 24. Mean haemoglobin levels increased by Week 2 and remained within normal range through to Week 24.

5.2 Pharmacokinetic properties

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 1,793 RA patients treated with a one-hour infusion of 4 and 8 mg/kg tocilizumab every 4 weeks for 24 weeks.

The following parameters (predicted mean \pm SD) were estimated for a dose of 8 mg/kg tocilizumab given every 4 weeks: steady-state area under curve (AUC) = 35000 \pm 15500 h μ g/ml, trough concentration (C_{min}) = 9.74 \pm 10.5 μ g/ml and maximum concentration (C_{max}) = 183 \pm 85.6 μ g/ml, and the accumulation ratios for AUC and C_{max} were small, 1.22 and 1.06, respectively. The accumulation ratio was higher for C_{min} (2.35), which was expected based on the non-linear clearance contribution at lower concentrations. Steady-state was reached following the first administration for C_{max} and after 8 and 20 weeks for AUC and C_{min} , respectively. Tocilizumab AUC, C_{min} and C_{max} increased with increase of body weight. At body weight \geq 100 kg, the predicted mean (\pm SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 55,500 \pm 14,100 μ g•h/ml, 19.0 \pm 12.0 μ g/ml, and 269 \pm 57 μ g/ml, respectively, which are higher than mean exposure values for the patient population (AUC = 35000 \pm 15500 h μ g/ml, C_{min} = 9.74 \pm 10.5 μ g/ml and C_{max} = 183 \pm 85.6 μ g/ml). The dose response curve for tocilizumab flattens at higher exposure, resulting in smaller efficacy gains for each incremental increase in tocilizumab concentration such that clinically meaningful increases in efficacy were not demonstrated in patients treated with > 800 mg of tocilizumab. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended (see section 4.2).

Distribution

In RA patients the central volume of distribution was 3.5 l, the peripheral volume of distribution was 2.9 l resulting in a volume of distribution at steady state of 6.4 l.

Elimination

Following intravenous administration, tocilizumab undergoes biphasic elimination from the circulation. The total clearance of tocilizumab was concentration-dependent and is the sum of the linear and non-linear clearance. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 12.5 ml/h. The concentration-dependent non-linear clearance plays a major role at low tocilizumab concentrations. Once the non-linear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.

The $t_{1/2}$ of tocilizumab was concentration-dependent. At steady-state following a dose of 8 mg/kg every 4 weeks, the effective $t_{1/2}$ decreased with decreasing concentrations within a dosing interval from 14 days to 8 days.

Linearity

Pharmacokinetic parameters of tocilizumab did not change with time. A more than dose-proportional increase in the AUC and C_{min} was observed for doses of 4 and 8 mg/kg every 4 weeks. C_{max} increased dose-proportionally. At steady-state, predicted AUC and C_{min} were 2.7 and 6.5 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively.

Special populations

Renal impairment: No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab has been conducted. Most of the patients in the population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (creatinine clearance based on Cockcroft-Gault $<$ 80 ml/min and \geq 50 ml/min) did not impact the pharmacokinetics of tocilizumab.

Hepatic impairment: No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab has been conducted.

Age, gender and ethnicity: Population pharmacokinetic analyses in adult RA patients, showed that age, gender and ethnic origin did not affect the pharmacokinetics of tocilizumab.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Carcinogenicity studies were not performed because IgG1 monoclonal antibodies are not deemed to have intrinsic carcinogenic potential.

Available non-clinical data demonstrated the effect of IL-6 on malignant progression and apoptosis resistance to various cancer types. These data do not suggest a relevant risk for cancer initiation and progression under tocilizumab treatment. Additionally, proliferative lesions were not observed in a 6-month chronic toxicity study in cynomolgus monkeys or in IL-6-deficient mice.

Available non-clinical data do not suggest an effect on fertility under tocilizumab treatment. Effects on endocrine active and reproductive

system organs were not observed in a chronic cynomolgus monkey toxicity study and reproductive performance was not affected in IL-6-deficient mice. Tocilizumab administered to cynomolgus monkeys during early gestation, was observed to have no direct or indirect harmful effect on pregnancy or embryonal-foetal development. However, a slight increase in abortion/embryonal-foetal death was observed with high systemic exposure ($>$ 100 x human exposure) in the 50 mg/kg/day high-dose group compared to placebo and other low-dose groups. Although IL-6 does not seem to be a critical cytokine for foetal growth or the immunological control of the maternal/foetal interface, a relation of this finding to tocilizumab cannot be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Polysorbate 80
Disodium phosphate dodecahydrate
Sodium dihydrogen phosphate dihydrate
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial: 30 months

Diluted product: After dilution, the prepared solution for infusion is physically and chemically stable in sodium chloride 9 mg/ml (0.9%) solution for injection at 30°C for 24 hours.

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C–8°C, unless dilution has taken place in controlled and validated aseptic conditions.

RoACTEMRA is supplied as a sterile concentrate that does not contain preservatives.

6.4 Special precautions for storage

Store vials in a refrigerator (2°C–8°C). Do not freeze.

Keep the vial(s) in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product see section 6.3.

6.5 Nature and contents of container

RoACTEMRA is supplied in a vial (type I glass) with a stopper (butyl rubber) containing 4 ml, 10 ml or 20 ml concentrate. Pack sizes of one and four vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for dilution prior to administration

Parenteral medicinal products should be inspected visually for particulate matter or discoloration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted.

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 RoACTEMRA concentrate required for the patients dose, under aseptic conditions. The required amount of RoACTEMRA 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.

RoACTEMRA is for single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
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Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/492/001
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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 January 2009

10. DATE OF REVISION OF THE TEXT

4 June 2010

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu/>.