
ACTEMRA®



Tocilizumab

1. DESCRIPTION

1.1 Therapeutic/Pharmacologic Class of Drug

Tocilizumab is a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass.

1.2 Type of Dosage Form

Concentrate for solution for infusion.

1.3 Route of Administration

Intravenous (i.v.) infusion.

1.4 Sterile/Radioactive Statement

Sterile.

1.5 Qualitative and Quantitative Composition

Active ingredient: tocilizumab.

Tocilizumab is a clear to opalescent, colourless to pale yellow liquid, supplied in preservative-free, non-pyrogenic single-use vials.

Tocilizumab is supplied in 10 ml and 20 ml vials containing 4 ml, 10 ml or 20 ml of Tocilizumab (20 mg/ml).

Excipients: Polysorbate 80, sucrose, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate and water for injections.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

○The following diseases which do not show sufficient response to the existing therapies: Rheumatoid arthritis (RA) (including inhibition of progression of structural joint damage), polyarticular-course juvenile idiopathic arthritis (pJIA), and systemic juvenile idiopathic arthritis (sJIA)

○Improvement of various symptoms (e.g. generalised fatigue) and laboratory findings (increased C-reactive protein, fibrinogen, and erythrocyte sedimentation rate, decreased haemoglobin and albumin) associated with Castleman's disease.

2.2 Dosage and Administration

RA and pJIA: The recommended dose of tocilizumab is 8 mg/kg as a single intravenous drip infusion administered at 4-week intervals.

sJIA and Castleman's disease: The recommended dose of tocilizumab is 8 mg/kg as a single intravenous drip infusion administered at 2-week intervals. The dosing interval can be shortened to a minimum of 1 week depending on the patient's disease condition.

2.3 Contraindications

ACTEMRA® is contraindicated in the following patients

- (1) Patients with a concurrent serious infection (treatment with ACTEMRA® may exacerbate a preexisting infection).
- (2) Patients with known hypersensitivity to tocilizumab or any other component of the product.

2.4 Warnings and Precautions

Precautions related to INDICATIONS

RA and pJIA:

ACTEMRA® should be administered to patients who have failed to show sufficient response in the past despite receiving appropriate treatment with one or more DMARD.

sJIA:

1. ACTEMRA® should be administered to patients who have failed to show sufficient response in the past despite receiving appropriate treatment with corticosteroids.
2. Macrophage activation syndrome (MAS) may develop as a serious concomitant disease in sJIA patients. The treatment of MAS should take priority, and ACTEMRA® treatment should not be started in patients with concomitant MAS. If MAS occurs while a patient is receiving ACTEMRA®, treatment with ACTEMRA® should be discontinued, and an appropriate treatment for MAS should be given immediately.

Precautions related to DOSAGE AND ADMINISTRATION

Since anti-tocilizumab antibodies may develop if ACTEMRA® is administered in a patient whose serum tocilizumab level is not continuously maintained, the “DOSAGE AND ADMINISTRATION” should be strictly adhered.

sJIA: The dosing interval can be shortened, but this is limited to cases in which improvement of symptoms is insufficient and the suppression of IL-6 effects is assessed to be insufficient as indicated by the CRP level.

Castleman’s disease: The CRP level should be determined at each administration. The dosing interval can be shortened as indicated by the CRP level, but this is limited to cases in which the improvement of symptoms is assessed to be insufficient.

Dilution: Tocilizumab should be diluted to 100 ml by a healthcare professional with sterile 0.9% w/v sodium chloride solution using aseptic technique (50ml for patients weighing less than 25kg or less). Tocilizumab is recommended for i.v. infusion over 1 hour.

Administration:

- (1) ACTEMRA® should be administered through an in-line filter.
- (2) Intravenous infusion of ACTEMRA® should be initiated slowly while closely monitoring the patient’s condition. After confirming that there is no sign or symptom of a

reaction in the patient, the speed of the infusion can be accelerated so that the administration is completed in about 1 hour.

Careful Administration (ACTEMRA® should be administered with care in the following patients.)

(1) Patients with concurrent active infection or suspected infection (treatment with ACTEMRA® may exacerbate preexisting infections.)

(2) Patients with previous tuberculosis (in particular, patients with a history of tuberculosis and patients with findings of healed tuberculosis on chest X-rays) [Since the possibility of progression to active tuberculosis cannot be ruled out, periodical chest X-rays, etc. should be performed while due care should also be taken for the onset of tuberculosis symptoms]

(3) Patients in an immune compromised state (ACTEMRA® therapy may induce infection.)

(4) Patients with an intestinal diverticulum

Important Precautions

(1) Treatment with ACTEMRA® may induce anaphylactic shock or an anaphylactoid reaction. Appropriate measures including medications (with epinephrine, corticosteroids, antihistamines, etc.) and an emergency procedure should be made ready for immediate use. If any symptom or sign of a reaction appears, ACTEMRA® infusion should be discontinued immediately.

(2) Infusion reactions, such as fever, chills, nausea, vomiting, headache, and rash, may occur during or on the same day following the administration of ACTEMRA®. The patient's condition should be closely monitored for possible reactions. If any symptom or sign of a reaction appears, ACTEMRA® infusion should be discontinued immediately and appropriate measures (administration of an antihistamine, antipyretics/analgesics, etc.) should be taken.

(3) When used in patients with concomitant infections, treatment with ACTEMRA® may exacerbate preexisting infections, so caution should be taken for the following points.

1) Prior to starting treatment with ACTEMRA®, the presence or absence of infections including pneumonia should be checked. It should be noted that the clinical symptoms of Castleman's disease, sJIA, pJIA, and RA (fever, malaise, lymphadenopathy, etc.) are similar to the clinical symptoms of infection, so thorough differentiation is required.

2) Opportunistic infections may occur in immune compromised patients. Thus, initiation of ACTEMRA® treatment is not recommended in these patients. ACTEMRA® treatment should not be initiated in patients with persisting decreased lymphocyte counts (Reference value: 500/ μ L).

3) In patients with concomitant infections, treatment of the infections should be given priority over treatment with ACTEMRA®.

(4) ACTEMRA® may suppress acute phase reactions (fever, increase in C-reactive protein, etc.) and infection symptoms, and may result in delaying the detection of infection. Therefore, WBC and Neutrophil counts should be determined periodically, and if an infection is suspected based on changes in these counts and symptoms such as stridor, cough or pharyngeal pain, a chest X-ray or CT scan, etc., should be conducted and appropriate measures should be taken even if no acute phase reaction is observed. Furthermore, patients should be instructed to be cautious of symptoms and signs of not only respiratory infections, but also of skin infections and urinary tract infections, and to consult their physician immediately when they notice any abnormality.

(5) It can not be ruled out that symptoms of tuberculosis may appear or tuberculosis may be exacerbated in patients with previous tuberculosis. Thus, before administering ACTEMRA® the patient should be thoroughly checked for the presence of tuberculosis, such as by interviewing for tuberculosis, chest X-ray, and tuberculin test, and, if appropriate, by chest CT, etc. In particular, patients who are suspected of being infected with tuberculosis should be adequately checked for the presence of infection using multiple tests, and a physician experienced in tuberculosis treatment should be consulted. Furthermore, treatment of tuberculosis should be given priority over treatment with ACTEMRA® in patients who have been confirmed to have active tuberculosis. Patients should be instructed to consult their physician immediately if they have any symptoms that they suspect to be tuberculosis (persistent cough, fever, etc.).

(6) Live vaccines should not be given to patients during treatment with ACTEMRA® because of the potential for live vaccines to cause infection.

(7) Pleurisy (including cases that could not be specified as infectious) has been reported in clinical studies. If pleurisy (characteristic findings: pleural effusion, chest pain, dyspnoea, etc.) is observed during the treatment with ACTEMRA®, a complete pathogenetic differentiation should be performed, and appropriate measures should be taken with consideration also given to non-infectious cases.

(8) Since there may be occurrences of abnormal lipid parameters, such as increased total cholesterol, triglycerides, and/or LDL cholesterol, lipid tests should be conducted about 3 months after the start of treatment and as needed thereafter. When judged clinically necessary, appropriate measures such as administration of an antihyperlipidemic drug should be taken.

(9) When ACTEMRA® is used concomitantly with drugs with a hepatotoxic potential, or in patients with active hepatic disease or hepatic impairment, patients should be closely monitored, such as by careful observation for elevations in hepatic transaminases levels, and if any abnormality is observed, appropriate measures such as discontinuation of treatment with ACTEMRA® should be taken (see “Other Precautions”).

(10) sJIA and Castleman’s disease: Following temporary or permanent discontinuation of treatment with ACTEMRA®, the biological actions of IL-6 may be excessively

expressed, which may exacerbate the pathological state. The additional use or increased dose of a corticosteroid or other appropriate measures should be considered as necessary.

(11) Cardiac abnormalities have been observed in clinical studies. Therefore, close monitoring of the patient's condition should be conducted, as needed with electrocardiography, blood test, echocardiography, etc., and in the case of patient with concurrent heart disease, electrocardiography should be conducted periodically, with careful monitoring of changes during treatment with ACTEMRA®.

Precautions Concerning Use

(1) When ACTEMRA® is prepared

1.1) Vials containing ACTEMRA® should not be mixed vigorously during and after dilution. Solutions of ACTEMRA® can foam up easily because it contains polysorbate.

1.2) ACTEMRA® should be diluted just prior to administration and used promptly after dilution. The remaining solution should be discarded.

(2) When ACTEMRA® is administered

2.1) ACTEMRA® should only be administered as an intravenous infusion, not as a subcutaneous or intramuscular injection.

2.2) ACTEMRA® should be administered through independent intravenous tubing with a sterile pyrogen-free in-line filter (with pore sizes not greater than 1.2 microns).

2.3) ACTEMRA® should not be mixed with any other injection or infusion preparation.

Other Precautions

(1) The emergence of anti-tocilizumab antibodies has been reported in clinical studies (RA: 18 of 601 patients (3.0 %), pJIA: 1 of 19 patients (5.3 %), sJIA: 11 of 128 patients (8.6 %); and Castleman's disease: 1 of 35 patients (2.9%))

(2) In clinical studies in patients with rheumatoid arthritis, the incidence of elevated transaminase levels was higher in groups on ACTEMRA® + DMARD compared with ACTEMRA® alone. The incidences of elevated ALT (SGPT) or AST (SGOT) values more than three times upper limit of normal were 103 of 1582 patients (6.5%) on 8 mg/kg ACTEMRA® + DMARD and 18 of 1170 patients (1.5%) on placebo + DMARD; and the incidences in groups on a monotherapy were 6 of 288 patients (2.1%) on 8 mg/kg ACTEMRA® and 14 of 284 patients (4.9%) on MTX only. These abnormalities were observed transiently and not associated with hepatitis or hepatic failure.

(3) Safety has not been established for long-term treatment with ACTEMRA® beyond the periods used in clinical studies of ACTEMRA®, of 2.9 and 1.1 years (medians; treatment periods ranging from 0.1 to 8.1 and 0.1 to 2.8 years, respectively, in long-term treatment studies).

(4) IL-6 has been reported to suppress the development of drug metabolizing enzymes in the liver (CYPs) in *in vitro* studies conducted using human hepatocytes, though no change was observed in the expression of CYPs when IL-6 was added to human hepatocytes in the presence of tocilizumab). Furthermore, the expression of CYPs has also been reported to be suppressed by IL-6 overproduction in patients with an inflammatory reaction). Results of clinical studies in patients with rheumatoid arthritis suggest that there was an increase in expression of CYP3A4, CYP2C19 and CYP2D6

associated with the inhibition of IL-6 following treatment with ACTEMRA®. Therefore, the possibility cannot be ruled out that the effects of concomitant drugs may be reduced in association with the recovery of excess-IL-6 induced inhibition of CYP expression and improvement of the inflammatory response as a result of treatment with ACTEMRA®).

(5) It has been reported from studies in mice that gp130-mediated signal transduction plays some role in protecting cardiac muscle cells). Several cytokines including IL-6 are known to be involved in gp130-mediated signal transduction. In view of the fact that tocilizumab inhibits the biological activities of IL-6, the possibility that tocilizumab may affect the heart cannot be excluded.

(6) ACTEMRA® has shown neutralizing activity against human and cynomolgus monkey IL-6 receptors but not against mouse and rat IL-6 receptors. No carcinogenicity study has therefore been conducted

WARNINGS

1. Infections

ACTEMRA® has been associated with serious infections including sepsis and pneumonia, rarely with a fatal outcome. ACTEMRA® exerts its therapeutic effects by suppressing the actions of IL-6, a cytokine that induces acute phase reactions (fever, increase in C-reactive protein, etc.). Treatment with ACTEMRA® suppresses these reactions and accordingly suppresses signs and/or symptoms associated with infection, which may delay the detection of infections. As a result, it may potentially make the infection more serious. Therefore, close monitoring and inquiry into the patient's condition must be undertaken during treatment with ACTEMRA®. Changes in white blood cell and neutrophil counts should be carefully evaluated even when symptoms are mild and no acute phase reaction is observed. If infection is suspected, a chest X-ray or CT scan, etc., should be conducted and appropriate measures should be taken (see "Important Precautions" and "Clinically significant adverse drug reactions").

2. ACTEMRA® treatment should be started after the patient is thoroughly informed of the fact that adverse drug reactions such as serious infections may occur and that ACTEMRA® will not completely resolve their disease, and only when it is judged that the potential benefit of treatment outweighs the potential risk.

3. Before treatment with ACTEMRA® is given to patients with rheumatoid arthritis (RA) and polyarticular-course juvenile idiopathic arthritis (pJIA), use of one or more disease-modifying anti-rheumatic drugs (DMARDs) should be thoroughly considered.

ACTEMRA® should be used by a physician with sufficient knowledge of ACTEMRA® and experience with the treatment of RA and/or pJIA.

4. For patients with systemic juvenile idiopathic arthritis (sJIA), ACTEMRA® should be used by a physician with sufficient knowledge of ACTEMRA® and experience with the treatment of sJIA.

2.5 Interactions with other Medicinal Products and other Forms of Interaction

Population pharmacokinetic analysis revealed that concomitant use of medicinal products for rheumatoid arthritis did not influence the pharmacokinetics of tocilizumab, such as methotrexate, chloroquine and derivatives, immunosuppressants (azathioprine, leflunomide), corticosteroids (prednisone and derivatives), folic acid and derivatives, non-steroidal anti-inflammatory drugs (diclofenac, ibuprofen, naproxen, meloxicam, COX-2 inhibitors (celecoxib)), analgesics (paracetamol, codeine and derivatives, tramadol).

Tocilizumab has not been studied in combination with other biological DMARDs. The formation of CYP450 enzymes is suppressed by the cytokines stimulating chronic inflammation. Thus it is expected that for any drug with a potent anti-inflammatory effect, such as tocilizumab, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation of tocilizumab, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect (eg, warfarin) or drug concentration (eg, cyclosporine) should be performed and the individual dose of the medicinal product adjusted as needed.

2.6 Use in Special Populations

2.6.1 Geriatric Use

Since physiological function is generally reduced in the elderly, ACTEMRA® should be carefully administered while closely monitoring the patient's condition.

2.6.2 Pregnancy, Delivery or Lactation

(1) The safety of ACTEMRA® has not been established in pregnant women. Tocilizumab has been reported to cross the placental barrier in cynomolgus monkeys. ACTEMRA® should be administered to women who are pregnant or may possibly be pregnant only when the potential benefit of treatment with ACTEMRA® is deemed to outweigh the potential risk of the therapy.

(2) The safety of ACTEMRA® has not been established in nursing mothers. Nursing should be discontinued during treatment with ACTEMRA®.

2.6.3 Pediatric Use

The safety of ACTEMRA® has not been established in low birth weight infants, neonates, or nursing infants (see "PHARMACOKINETICS").

2.7 Undesirable Effects

Of a total of 783 patients surveyed, there have been 751 patients (95.9%) with adverse drug reactions. The most frequently reported were 421 events (53.8 %) of nasopharyngitis, 292 events (37.3 %) of cholesterol increased, 148 events (18.9 %) of low density lipoprotein increased, 126 events (16.1 %) of triglycerides increased, and 119 events (15.2 %) of alanine aminotransferase increased, etc.

Clinically significant adverse drug reactions

1) **Anaphylactic shock or anaphylactoid reaction (0.4 %):** Anaphylactic shock or anaphylactoid reactions such as decreased blood pressure, dyspnea, loss of consciousness, dizziness, nausea, vomiting, pruritus, and hot flushes may occur in patients receiving ACTEMRA®. Therefore, the patient's condition should be closely monitored for these possible reactions during the infusion. If any symptom or sign of a reaction appears, ACTEMRA® infusion should be discontinued immediately, and appropriate measures such as administration of epinephrine, corticosteroids, or anti-histamines should be taken.

Patients with anaphylactic shock or anaphylactoid reactions should be closely followed up until the symptoms are resolved. After the administration of ACTEMRA®, the patient should be checked for any symptom or sign.

2) **Infections:** Serious infections including opportunistic infections, such as pneumonia [7.8%], herpes zoster [6.4%], infectious gastroenteritis [3.4%], cellulitis [3.3%], infectious arthritis [0.9%], sepsis [0.4%], and rarely, nontuberculous mycobacteriosis [0.4%], tuberculosis [0.3%], and *Pneumocystis jirovecii* pneumonia [0.1%], etc., may occur, with a fatal outcome. While on treatment with ACTEMRA®, the patient's condition should be closely monitored, and if any abnormality is observed, appropriate measures such as the discontinuation of treatment should be taken.

3) **Intestinal perforation:** Intestinal perforation has been reported. ACTEMRA® may suppress symptoms (abdominal pain, fever, etc.) of acute abdomen such as diverticulitis, etc., and may result in delaying the detection of acute abdomen leading to perforation. Therefore, if any abnormality is observed, appropriate measures, such as examination of abdominal X-rays or CT scan, should be taken.

4) **Neutropenia (7.0%):** Since neutropenia may occur, patients should be closely monitored, and if any abnormality is observed, appropriate measures such as the discontinuation of treatment with ACTEMRA® should be taken.

5) **Cardiac failure:** Since cardiac failure has been reported in patients receiving ACTEMRA®, the patient's condition should be closely monitored for possible cardiac failure. If any sign or symptom of cardiac failure develops, appropriate measures such as the discontinuation of treatment with ACTEMRA® should be taken.

Other adverse drug reactions

If any of the following adverse drug reactions occur, appropriate measures such as temporary or permanent discontinuation should be taken.

	≥5%	≥1% to <5%	≥0.5% to <1%
Resistance mechanism	Herpes virus infection	Influenza, oral candidiasis	Parotitis, wound infection
Respiratory system	Upper respiratory tract infections [nasopharyngitis, upper respiratory tract inflammation, etc.] (90.0%), bronchitis, pharyngolaryngeal pain, cough, sinusitis	Rhinitis, rhinorrhoea, pharyngeal erythema	Pleurisy, bronchiectasis, nasal congestion, epistaxis, haemoptysis, asthma, pharynx discomfort
Metabolism	Cholesterol increased (37.3%), triglycerides increased, low density lipoprotein increased, high density lipoprotein increased, blood lactate dehydrogenase increased	Hyperlipidaemia, hypercholesterolaemia, blood uric acid increased, creatine phosphokinase increased, protein total decreased, blood potassium decreased	Blood sugar increased, diabetes mellitus aggravated, blood phosphorus increased/decreased, serum ferritin decreased, blood calcium decreased
Hepatic	Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased	Hepatic steatosis, bilirubin increased, alkaline phosphatase increased	Hepatic function abnormal, cholelithiasis
Cardiovascular	Hypertension, blood pressure increased	T wave inversion/amplitude decreased, palpitation, blood pressure decreased	Supraventricular/ventricular extrasystoles, ST segment elevation/depression, T wave amplitude increased
Blood-coagulation system	White blood cell count decreased	Lymphadenitis, anaemia, lymphocyte count decreased, platelet count decreased, fibrinogen decreased, eosinophil count increased, white blood cell count increased, fibrin degradation products [FDP, D dimer] increased, haematocrit decreased, haemoglobin decreased	Lymph nodes swollen, thrombin-antithrombin III complex increased, neutrophil count increased, red blood cell count decreased,

Gastrointes- tinal	Gastroenteritis, stomatitis, diar- rhea, abdominal pain, constipation	Nausea, vomiting, abdominal dis- comfort, gastritis, cheilitis, enteroco- litis, gastric/colonic polyp, reflux oe- sophagitis	Abdominal distension, haemor- rhoids, dyspepsia, thirst, glossitis, anorexia, gastric ulcer
		Periodontitis, dental caries, gingivitis, toothache	Periodontal infection
Psychoneu- rologic	Headache	Dizziness, hypoaesthesia, insomnia,	Neuropathy peripheral
Ear		Otitis media, vertigo	Sudden hearing loss, otitis ex- terna, ear discomfort, tinnitus
Eye	Conjunctivitis	Hordeolum, chalazion, dry eye, con- junctival haemorrhage	Cataract, vitreous floaters, ble- pharitis, retinal haemorrhage
Skin	Rash[eczema, prurigo, rash popular, etc.], tinea, pruritus, skin infection, nail infection	Abscess, urticaria, skin ulcer, in- growing nail, haemorrhage subcuta- neous, acne, keratosis, dry skin	Blister, dermal cyst
Muscu- loskeletal		Back pain, myalgia [myalgia, shoul- der muscle stiffness], arthralgia, pain in extremity, osteoporosis, bone den- sity decreased	Neck pain, juvenile arthritis ag- gravated
Urinary sys- tem	Cystitis	Urinary tract infection, kidney stone, blood urea nitrogen increased, red blood cells urine positive, sugar in urine, protein urine, N-acetyl-β-D-glucosaminidase in- creased	Pollakiuria, pyelonephritis, white blood cells urine positive
Reproduc- tive system		Vaginal infection	Genital haemorrhage, cervical polyp
Others		Pyrexia, oedema, malaise, chills, chest pain, chest discomfort, feeling hot, seasonal allergy, rhinitis allergic, immunoglobulin G decreased, anti- nuclear antibody positive* ⁵⁾	Thrombophlebitis, flushing, C-reactive protein increased, DNA antibody positive* ⁵⁾ , rheumatoid factor positive, weight increased

2.8 Overdose

There are limited data available on overdosage with tocilizumab. One case of accidental overdose was reported in which a patient with multiple myeloma received a single dose of 40 mg/kg. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received a single dose up to 28 mg/kg, although doselimiting neutropenia was observed.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacology

1. *In vitro* studies have demonstrated that tocilizumab binds to both soluble and membrane bound IL-6 receptors and blocks the biological activities of IL-6)
2. Tocilizumab suppresses the biological activities of human IL-6 given to cynomolgus monkeys.)
3. In a cynomolgus monkey CIA (Collagen Induced Arthritis) model, tocilizumab suppressed the onset of joint swelling by intravenous injection before the onset of arthritis, and improved swollen joints by intravenous injection after the onset of arthritis)
4. Anti-murine IL-6 receptor antibody inhibited the onset of anemia, proteinuria, and hypergammaglobulinemia, etc., according to the findings, and prolonged the survival duration in IL-6 transgenic mice)

3.2 Pharmacokinetics

1. Serum Concentrations

(1) Phase I study (single dose)

A single dose of tocilizumab was administered (intravenous infusion over 1 hour) at doses of 0.15, 0.50, 1.0, or 2.0 mg/kg to a total of 20 healthy adult men, 5 in each dose level. The C_{max} increased dose-dependently, whereas, with increase in dose, the total body clearance (CL_{total}) decreased and the half-life ($t_{1/2}$) and the mean residence time (MRT) were prolonged significantly. A non-linear pharmacokinetic profile of tocilizumab was confirmed for the dose range examined (Table 1).

Table 1 Pharmacokinetic parameters following a single dose

Dose (mg/kg)	C_{max} ($\mu\text{g/mL}$)	AUC_{finite} ($\text{hr}\cdot\mu\text{g/mL}$)	$t_{1/2}$ (hr)	CL_{total} (mL/hr/kg)	MRT (hr)	Vd_{ss} (mL/kg)
0.15	2.4 ± 0.6	11 ± 6	17 ± 16	3.8 ± 2.3	25 ± 22	63.4 ± 16.6
0.50	8.5 ± 1.2	285 ± 73	33 ± 4	1.3 ± 0.2	47 ± 5	58.4 ± 7.1
1.0	19.5 ± 2.7	1009 ± 222	49 ± 5	0.8 ± 0.1	69 ± 8	57.3 ± 10.9
2.0	37.6 ± 8.8	2532 ± 569	74 ± 9	0.6 ± 0.2	107 ± 16	65.9 ± 8.3

(n=5, mean ± SD)

(2) Pharmacokinetics in patients with rheumatoid arthritis (RA)

1) Single dose study

Tocilizumab was administered (intravenous infusion over 1 hour) as a single dose at a dose of 8 mg/kg to 31 patients with RA. The serum tocilizumab concentrations are shown in Fig. 1. The pharmacokinetic parameters (mean ± SD) were as follows:

$AUC_{finite} = 19852 \pm 5749 \text{ hr}\cdot\mu\text{g/mL}$, $t_{1/2} = 133 \pm 25.7 \text{ hr}$, $CL_{total} = 0.4 \pm 0.1 \text{ mL/hr/kg}$, and $Vd_{ss} = 78.5 \pm 16.8 \text{ mL/kg}$.

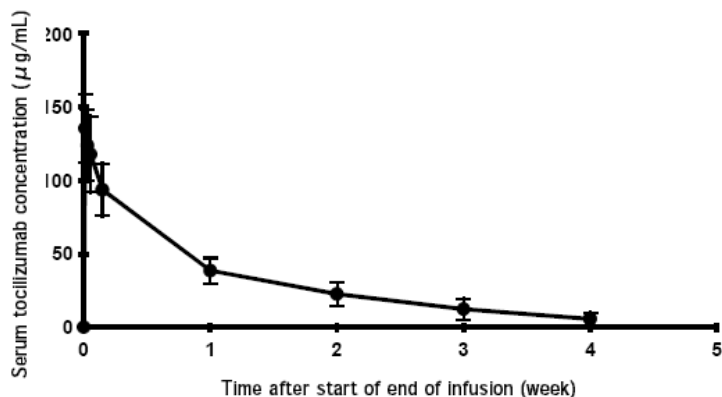


Fig. 1. Time course of serum tocilizumab concentration after a single dose in patients with RA (mean \pm SD)

2) Repeated dose studies

i) Evaluation of dose-dependency

Tocilizumab was administered (intravenous infusion over 2 hours) at a dose of 2, 4, or 8 mg/kg at 2-week intervals to 15 patients with RA (5 patients included in each dose group). The CL_{total} decreased in a dose-dependent manner, while the $t_{1/2}$ was significantly prolonged. A non-linear pharmacokinetic profile was confirmed by these results (Table 2).

Table 2 Pharmacokinetic parameters following repeated administration in patients with RA

Number of doses	Dose (mg/kg)	C_{1hr} ($\mu\text{g/mL}$)	AUC_{finite} ($\mu\text{g}\cdot\text{hr/mL}$)	$t_{1/2}$ (hr)	CL_{total} (mL/hr/kg)	MRT (hr)	$V_{d_{ss}}$ (mL/kg)
1	2	43.6 \pm 10.1	3440 \pm 823	74 \pm 18	0.5 \pm 0.2	107 \pm 25	55.0 \pm 13.0
	4	49.0 \pm 12.6	4663 \pm 2185	97 \pm 50	0.9 \pm 0.5	138 \pm 68	102 \pm 24.0
	8	82.5 \pm 32.4	10661 \pm 4070	160 \pm 34	0.6 \pm 0.2	227 \pm 46	137 \pm 31.6
3	2	27.9 \pm 12.3	3014 \pm 1070	87 \pm 18	0.5 \pm 0.1	140 \pm 26	70.7 \pm 13.5
	4	49.5 \pm 10.1	6035 \pm 3200	140 \pm 71	0.7 \pm 0.5	204 \pm 105	98.5 \pm 14.6
	8	129.9 \pm 48.1	19939 \pm 8900	242 \pm 71	0.3 \pm 0.1	343 \pm 105	90.9 \pm 29.9

(n=4-5, mean \pm SD)

ii) Phase III study

Tocilizumab at a dose of 8 mg/kg was administered (intravenous infusion over 1 hour) 13 times at 4-week intervals to 157 patients with RA. The serum tocilizumab concentration increased from the initial dose on and the trough concentration (mean \pm SD) at 4 weeks after the 3rd (12 weeks after the initial dose) and 6th doses (24 weeks after the initial dose) reached 9.8 \pm 7.5 $\mu\text{g/mL}$ and 12.3 \pm 8.6 $\mu\text{g/mL}$, respectively. Values maintained almost constant levels from 20 weeks after the initial dose (Figure 2).

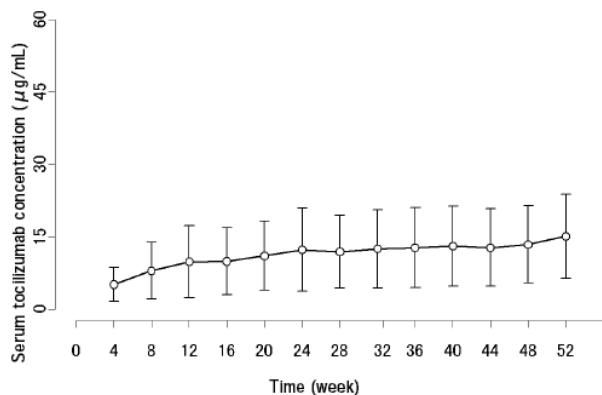


Fig.2. Time course of serum concentrations of tocilizumab (trough: immediately before infusion) in patients with RA given repeated doses of tocilizumab (mean \pm SD)

(3) Pharmacokinetics in patients with polyarticular-course juvenile idiopathic arthritis (pJIA)

Tocilizumab at a dose of 8 mg/kg was administered (intravenous infusion over 1 hour) three times at 4-week intervals to 19 patients (age: 3-19 yr; median: 12 yr) with pJIA. A comparison of pharmacokinetic parameters of serum Tocilizumab concentrations after the initial infusion are shown in Table 3. There are some patients in the group aged less than 7 years who showed a faster rate of elimination of serum tocilizumab.

Table 3. Pharmacokinetic parameters following repeated administration in patients with pJIA

Age	C_{1hr} (µg/mL)	AUC_{finite} (µg·hr/mL)	$t_{1/2}$ (hr)	CL_{total} (mL/hr/kg)	MRT (hr)	Vd_{ss} (mL/kg)
3 to <7	107.8 \pm 15.0	12970 \pm 2511	N.A.	N.A.	N.A.	N.A.
7 to <15	158.6 \pm 34.4	20878 \pm 5328	99 \pm 12	0.3 \pm 0.0	150 \pm 9	48.0 \pm 7.0
≥ 15	158.1 \pm 36.2	25954 \pm 6157	143 \pm 43	0.3 \pm 0.1	200 \pm 49	60.5 \pm 12.2
All	145.0 \pm 37.5	25275 \pm 6722	123 \pm 41	0.3 \pm 0.1	178 \pm 46	58.3 \pm 13.9

(Mean \pm SD, N.A.: not calculated)

(3 to <7 years: C_{1hr} and AUC_{finite} : n=5, 7 to <15 years: C_{1hr} and AUC_{finite} n=7, other parameters: n=4, ≥ 15 : n=7)

(4) Pharmacokinetics in patients with systemic juvenile idiopathic arthritis (sJIA)

Tocilizumab was administered (intravenous infusion over 1 hour) three times at 2-week intervals at a dose of 8 mg/kg to patients with sJIA (age: 2-19 yr; median: 8 yr), and thereafter, for those who showed response to treatment, tocilizumab was administered a further six times (total nine times, 18 weeks after initial administration).

Pharmacokinetic parameters after the initial and 3rd infusions are shown in Table 4. There are some patients in the group aged less than 7 years who showed a faster rate of elimination of serum tocilizumab.

The time course of serum tocilizumab concentration was considered to have reached a steady state during the period from week 8 through week 14 following the initial dose,

and the trough concentration was measured to be 57.4 µg/mL (18 weeks after the initial dose, n=13).

Serum tocilizumab levels were eliminated at a faster rate in some patients with a low body weight, height, or age.

Table 4. Pharmacokinetic parameters following repeated administration in patients with sJIA

Age	Number of doses	C _{1hr} (µg/mL)	AUC _{finite} (µg·hr/mL)	t _{1/2} (hr)	CL _{total} (mL/hr/kg)	MRT (hr)	Vd _{ss} (mL/kg)
2 to <7	1	142.8 ± 31.6	17677 ± 5193	N.A.	N.A.	N.A.	N.A.
	3	171.7 ± 51.2	23706 ± 9704	100 ± 38	0.3 ± 0.1	155 ± 60	45.4 ± 7.6
7 to <15	1	176.7 ± 48.5	24701 ± 7611	N.A.	N.A.	N.A.	N.A.
	3	239.8 ± 70.2	35333 ± 11668	127 ± 26	0.2 ± 0.2	188 ± 49	43.0 ± 17.5
≥15	1	166.0 ± 31.8	23653 ± 3571	N.A.	N.A.	N.A.	N.A.
	3	214.0 ± 40.0	33336 ± 8115	139 ± 30	0.2 ± 0.0	249 ± 21	43.6 ± 11.2

(Mean ± SD, N.A.: not calculated)

(2 to <7 years: n=19-23, 7 to <15 years: n=25-28, ≥15: n=4-5)

(5) Pharmacokinetics in patients with Castleman's disease

Repeated dose study

Tocilizumab was administered (intravenous infusion over 1 hour) eight times at 2-week intervals at a dose of 8 mg/kg to 28 patients with Castleman's disease. The mean serum tocilizumab concentration was 36.6 ± 17.5 µg/mL immediately before the eighth dose, with concentrations showing an increase from the initial dose. The t_{1/2} and MRT were prolonged up to the sixth dose after the initial dose and values maintained almost constant levels from the sixth dose (Table 5).

Table 5. Pharmacokinetic parameters following repeated administration in patients with Castleman's disease

Dose (mg/kg)	Number of doses	C _{1hr} (µg/mL)	AUC _{finite} (µg·hr/mL)	t _{1/2} (hr)	CL _{total} (mL/hr/kg)	MRT (hr)	Vd _{ss} (mL/kg)
8	1	112.9 ± 24.7	13092 ± 3254	99.7 ± 17.1	0.6 ± 0.2	145 ± 26.8	80.1 ± 15.0
	8	192.3 ± 38.7	28423 ± 7410	139 ± 37.4	0.2 ± 0.1	205 ± 54.2	46.8 ± 8.8

(n=26-28; mean ± SD)

2. Excretion

When tocilizumab was intravenously infused over 1 hour at doses of 0.15, 0.50, 1.0, or 2.0 mg/kg to a total of 20 healthy adult men, 5 in each dose level, tocilizumab was not excreted in urine at any of the doses examined. This indicates that the primary elimination of tocilizumab is via an extra-renal pathway.

3.3 Clinical/Efficacy Studies

1. Rheumatoid Arthritis (RA)

(1) Phase III double-blind comparative study

Methotrexate 8 mg/week + tocilizumab placebo (placebo group) or methotrexate placebo + tocilizumab 8 mg/kg/day (Tocilizumab group) was administered for 24 weeks in a double-blind comparative study to patients with RA with inadequate response to methotrexate. Results are shown below.

1) Reduction of signs and symptoms

At the last observation, ACR20 response (The American College of Rheumatology (ACR) definition of improvement in disease activity in RA) was confirmed in 80.3% of the tocilizumab group, which was significantly higher than that of the placebo group (25.0%; P<0.001).

Table 1. ACR20 Improvement Rates

	Placebo ^{NOTE)}	Tocilizumab	P-value
Number of patients	64	61	
ACR20	25.0%	80.3%	<0.001

NOTE) methotrexate administered 8 mg/week

2) Improvement in activities of daily living (ADL)

Evaluation of improvement in activities of daily living (ADL) from before administration to the last observation by MHAQ score (indicator of degree of activity limitation and nursing care necessity, etc.) showed a significant reduction of mean MHAQ by 0.32 in the tocilizumab group compared with 0.01 in the placebo group (P<0.001). Furthermore, MCID (minimum clinically important difference), defined as reduction exceeding 0.22, was observed in 67.2% of the tocilizumab group, which was significantly higher than the rate in the placebo group (34.4%) (P<0.001).

(2) Phase III randomized, comparative study

Tocilizumab was administered at 4-week intervals at a dose of 8 mg/kg and DMARDs or immunosuppressants (the patient's current RA treatment, control group) were continuously administered for 52 weeks in a randomized, comparative study of patients who showed inadequate response with DMARDs or immunosuppressants. Results are shown below.

1. Inhibition of progression of structural joint damage

Progression of joint destruction from before administration up to 52 weeks after administration was assessed by X-ray score (Modified Sharp Score) of the hands and feet, and the results are shown below. The total Sharp score was increased by 2.34 in the tocilizumab group compared with 6.12 in the control group, and progression of joint destruction was significantly retarded compared with the control group (P=0.001).

Table 2 Change in each score by Modified Shape Score 52 weeks after administration

	Existing therapy	Tocilizumab	P-value
Number of patients	143	157	
Bone erosion	3.21 (1.0)	0.85 (0.0)	<0.001
Joint space narrowing	2.91 (1.0)	1.49 (0.0)	0.024
Total	6.12 (2.5)	2.34 (0.5)	0.001

[(): median]

2. Polyarticular-course Juvenile Idiopathic Arthritis (pJIA)

Nineteen patients with pJIA were administered 8 mg/kg tocilizumab three times at 4-week intervals. Improvement of 30%, 50%, and 70% in the JIA criteria at the last observation was seen in respectively 94.7%, 94.7%, and 57.9% of patients, showing clear improvement of their underlying disease.

3. Systemic Juvenile Idiopathic Arthritis (sJIA)

○Phase III study - Blind period

Either tocilizumab (n=20) or placebo (n=23) was administered six times at 2-week intervals in a double-blind controlled study to the 43 eligible patients who showed an improvement of 30% or higher according to the JIA criteria and an improvement in CRP level of less than 0.5 mg/dL in the open period of the phase III study in which tocilizumab was administered three times at 2-week intervals at a dose of 8 mg/kg to 56 patients with sJIA. The maintenance rate and period of improvement rate of 30% or higher and CRP level of 1.5 mg/dL or less were compared. The rate of maintained response was 80.0% in the tocilizumab group, which was significantly higher than that in the placebo group (17.4%) (P<0.001). Similarly, the period in which response was maintained was also significantly longer in the tocilizumab group than in the placebo group (P<0.001).

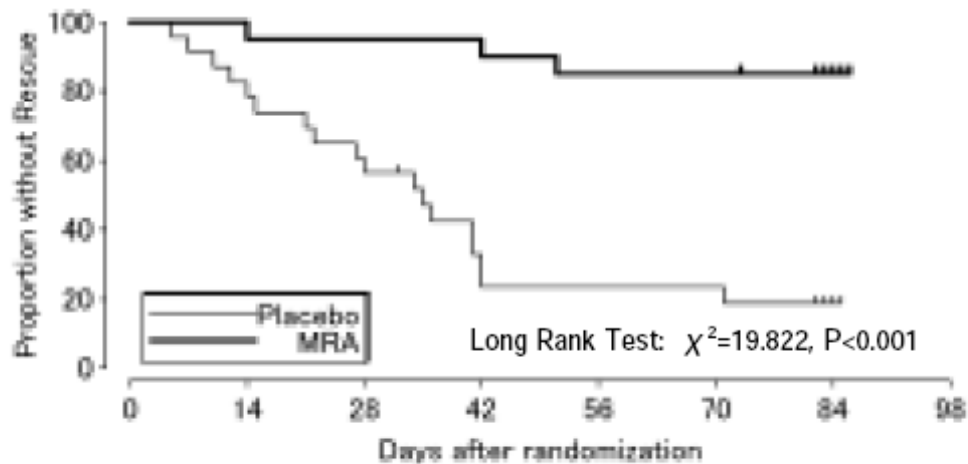


Fig. Time course of rates of maintained response (Kaplan-Meier curve)

4. Castleman's disease

(1) Phase II study

1) Stage I

To evaluate the efficacy of tocilizumab, the drug was administered intravenously at doses of 2, 4, and 8 mg/kg by inpatient ascending dose to seven patients with Castleman's disease. Each dose was given three times at 2-week intervals. At doses of 2 and 4 mg/kg, inflammatory markers such as CRP decreased 1 week after each administration; and in some patients, the markers increased again 2 weeks after administration. At a dose of 8

mg/kg, the tendency of the marker levels to decrease was sustained throughout the treatment period in almost all patients.

2) Stage II

Tocilizumab was administered eight times at a dose of 8 mg/kg at 2-week intervals to 28 patients with Castleman's disease. Inflammatory markers (CRP, fibrinogen, and ESR), generalised fatigue (evaluated by visual analog scale), anemia (Hb), and hypoalbuminemia, etc., significantly improved after the initial dose and throughout the treatment period (Table 3).

Table 3. Time course of efficacy endpoints (Stage II)

Variable	Baseline	From Week 6	From Week 16
CRP (mg/dL)	8.7 ± 5.0	1.2 ± 1.7**	0.9 ± 2.0**
Fibrinogen (mg/dL)	639 ± 188	356 ± 149**	317 ± 138**
ESR (mm/hr)	114 ± 34	63 ± 36**	48 ± 40**
Generalised fatigue (0-100 mm)	29.9 ± 22.8	17.4 ± 17.2*	17.7 ± 16.5**
Hb (g/dL)	9.2 ± 2.3	11.6 ± 1.9**	12.0 ± 2.1**
Albumin (g/dL)	2.7 ± 0.5	3.6 ± 0.5**	3.7 ± 0.5**

*P<0.05, **P<0.01, paired t test (n=24-28; mean ± SD)

(2) Extension study

Of the patients with Castleman's disease who participated in the Phase II studies, 33 continued to receive tocilizumab at a dose of 8 mg/kg, at 2-week intervals, in a long-term extension study (maximum: 1568 days; mean: 1191 days). As a result, therapeutic response, such as reduction in inflammatory marker levels, was maintained. Furthermore, in the seven patients in whom there was insufficient therapeutic response, inflammatory markers showed improvement when the dosing interval was shortened (to a minimum of one week).

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

This medicine should not be used after the expiry date (EXP) shown on the pack.

For vials: Store between 2 °C–8 °C, do not freeze. Keep the container in the outer carton in order to protect from light.

For prepared infusion solution: The prepared infusion solution of tocilizumab is physically and chemically stable in 0.9% w/v sodium chloride solution at 30 °C for 24 hours.

From a microbiological point of view, the prepared 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 not be longer than 24 hours at 2 °C–8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

4.2 Special Instructions for Use, Handling and Disposal

Withdraw the required amount of tocilizumab (0.4 ml/kg) under aseptic conditions and dilute to a calculated tocilizumab concentration in a 100 ml infusion bag containing sterile, non-pyrogenic 0.9% Sodium Chloride solution. To mix the solution, gently invert the bag to avoid foaming. Parenteral medications 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 must be infused.

4.3 Packs

Vials 80 mg/4 ml 1, 4

Vials 200 mg/10 ml 1, 4

Vials 400 mg/20 ml 1, 4

Current at September 2008 (based on April 2008, Version 6.0 of Actemra® Japanese approved package insert)

Made for

F. Hoffmann-La Roche Ltd, Basel, Switzerland

by **Chugai Pharma Manufacturing Co., Ltd, Utsunomiya-city, Japan**