Review Report

May 12, 2017
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Actemra 162 mg Syringe for SC Injection Actemra 162 mg Auto-injector for SC Injection
Non-proprietary Name	Tocilizumab (Genetical Recombination) (JAN*)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	August 25, 2016
Dosage Form/Strength	Injection: each 0.9 mL syringe contains 162 mg of Tocilizumab (Genetical Recombination). Injection: each 0.9 mL auto-injector contains 162 mg of Tocilizumab (Genetical Recombination).
Application Classification	Prescription drug, (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product (162 mg) at a reduced dosing interval has efficacy in the treatment of rheumatoid arthritis (RA) with an inadequate response to the product (162 mg) every 2 weeks, and has acceptable safety in view of its benefits (see Attachment). Since no new concerns have been identified regarding the safety of reduced dosing interval, as compared with the approved dosage regimen, the current safety measures should be continued.

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below.

Indication	Treatment of rheumatoid arthritis with an inadequate response to existing therapies (including the inhibition of progression of structural joint damage)

(No change)

Dosage and Administration	The usual adult dosage is 162 mg of Tocilizumab (Genetical Recombination) administered subcutaneously every 2 weeks. The dosing interval may be reduced to a minimum of 1 week in patients with an inadequate response.

(Underline denotes additions.)

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

April 10, 2017

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Product Submitted for Approval	
Brand Name	Actemra 162 mg Syringe for SC Injection Actemra 162 mg Auto-injector for SC Injection
Non-proprietary Name	Tocilizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	August 25, 2016
Dosage Form/Strength	Injection: each 0.9 mL syringe contains 162 mg of Tocilizumab (Genetical Recombination). Injection: each 0.9 mL auto-injector contains 162 mg of Tocilizumab (Genetical Recombination).
Proposed Indication	Treatment of rheumatoid arthritis with an inadequate response to existing therapies (including the inhibition of progression of structural joint damage) (No change)
Proposed Dosage and Administration	The usual adult dosage is 162 mg of Tocilizumab (Genetical Recombination) administered subcutaneously every 2 weeks. <u>The dosing interval may be reduced to a minimum of 1 week in patients with an inadequate response.</u> (Underline denotes additions)

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List of Abbreviations

ACR20 response rate, ACR50 response rate, ACR70 response rate	The proportion of patients achieving an ACR20, ACR50, or ACR70 response (American college of rheumatology 20, 50, 70 responder index)
BMI	Body mass index
CDAI	Clinical disease activity index
CRP	C-reactive protein
DAS28	Disease activity score based on 28 joint counts
DMARDs	Disease-modifying antirheumatic drugs
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
Fab	Fragment, antigen binding
FAS	Full analysis set
IgE	Immunoglobulin E
IL-6	Interleukin 6
Intravenous tocilizumab	Actemra 80 mg for Intravenous Infusion, Actemra 200 mg for Intravenous Infusion, Actemra 400 mg for Intravenous Infusion
LOCF	Last observation carried forward
OC	Observed cases
PMDA	Pharmaceuticals and Medical Device Agency
RA	Rheumatoid Arthritis

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Tocilizumab (Genetical Recombination) (hereinafter referred to as tocilizumab) is the active ingredient of "Actemra 162 mg Syringe for SC Injection and Actemra 162 mg Auto-injector for SC Injection" (subcutaneous tocilizumab) and "Actemra 80 mg for Intravenous Infusion, Actemra 200 mg for Intravenous Infusion, and Actemra 400 mg for Intravenous Infusion" (intravenous tocilizumab). Tocilizumab is a humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin G1 subclass, and was discovered through collaborative research by Osaka University and Chugai Pharmaceutical Co., Ltd. Subcutaneous tocilizumab has been approved for the "treatment of rheumatoid arthritis with an inadequate response to existing therapies (including the inhibition of progression of structural joint damage)," and intravenous tocilizumab for the "treatment of rheumatoid arthritis with an inadequate response to existing therapies (including the inhibition of progression of structural joint damage)" and other indications.

In the course of the development of subcutaneous tocilizumab, some data suggested that a reduced dosing interval (i.e., more often than every 2 weeks) may improve the efficacy of tocilizumab in some patients with rheumatoid arthritis (RA). The applicant therefore initiated a Japanese clinical study in May 2014 to assess a new dosage regimen. Based mainly on the results of the study, the applicant has submitted the present partial change application to modify the dosage and administration of subcutaneous tocilizumab.

As of April 2017, subcutaneous tocilizumab (including tocilizumab 162 mg once weekly) has been approved for the treatment of RA in 55 countries including the US and European countries.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Since the present application is for a new dosage, no data relating to the quality of tocilizumab were submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Although the application is for a new dosage, no new study data on non-clinical pharmacology were submitted because the non-clinical pharmacology of tocilizumab had been evaluated at the previous application.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although the application is for a new dosage, no new study data on non-clinical pharmacokinetics were submitted because the non-clinical pharmacokinetics of tocilizumab had been evaluated at the previous application.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is for a new dosage, no data relating to the toxicity of tocilizumab were submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Although the present application is for a new dosage, no new data on biopharmaceutic studies or associated analytical methods were submitted because the biopharmaceutic studies and associated analytical methods for tocilizumab had been evaluated at the previous application.

Serum tocilizumab concentrations were measured by an enzyme-linked immunoassay (ELISA) (lower limit of quantitation, 0.1 μg/mL). Serum antibodies against tocilizumab (i.e., anti-tocilizumab antibodies, anti-tocilizumab-antigen-binding fragment [Fab] antibodies, and anti-tocilizumab immunoglobulin E [IgE] antibodies) were measured by ELISA.

6.2 Clinical pharmacology

The applicant submitted new data for the present application: the results of a Japanese clinical study in patients with RA (CTD 5.3.5.1-1, -4, -12, and -13). Unless otherwise specified, the doses of Actemra are described as the doses of tocilizumab (genetical recombination) and pharmacokinetic parameters are expressed as mean ± standard deviation.

6.2.1 Japanese clinical study (CTD 5.3.5.1-1, -4, -12, and -13; Study MRA231JP [May 2014 to January 2017])

A double-blind, parallel-group study was conducted in 42 patients with RA who had an inadequate response to subcutaneous tocilizumab 162 mg every 2 weeks. The patients received subcutaneous tocilizumab 162 mg once weekly or every 2 weeks in the double-blind phase, and then once weekly for 40 weeks in the open-label phase. Table 1 shows changes in serum tocilizumab trough concentrations. At baseline, 4 patients in the once-weekly dosing (QW) group and 2 in the every-2-weeks dosing (Q2W) group were positive for anti-tocilizumab antibodies; 1 in the QW group and 1 in the Q2W group were positive for anti-tocilizumab-Fab antibodies; and 2 in the QW group and 1 in the Q2W group were positive for anti-tocilizumab IgE antibodies. Other than these patients, no patients developed anti-tocilizumab antibodies or anti-tocilizumab-Fab antibodies by Week 12, but 1 patient in the Q2W group developed anti-tocilizumab IgE antibodies by Week 12. In addition, 1 patient who switched from every 2 weeks (in the double-blind phase) to once weekly (in the open-label phase) developed anti-tocilizumab IgE antibodies. Neither of the 2 patients who developed anti-tocilizumab IgE antibodies during the

treatment period experienced administration-related systemic reactions, administration site reactions, or anaphylaxis that were considered attributable to the development of antibodies

Table 1. Serum tocilizumab trough concentrations in patients with RA treated with subcutaneous tocilizumab 162 mg (μg/mL)

		Double-blind phase						Open-label phase	
		Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	Week 24[c)]	Week 52[d)]
QW	n (n with a BLQ[a)] value)	21 (9)	20 (1)	21 (1)	19 (0)	19 (0)	19 (0)	17 (1)	13 (1)
	Serum concentration (μg/mL)	3.81 ± 3.71	7.12 ± 6.56	10.5 ± 7.87	14.4 ± 11.6	18.3 ± 15.2	19.7 ± 14.3	22.2 ± 17.4	27.6 ± 14.3
Q2W	n (n with a BLQ[a)] value)	21 (7)	20 (2)	19 (6)	17 (4)	17 (4)	17 (4)	15 (0)	14 (0)
	Serum concentration (μg/mL)	2.49 ± 3.48	6.30 ± 4.14[b)]	3.00 ± 3.14	3.11 ± 2.91	2.60 ± 2.46	3.94 ± 3.12	27.1 ± 15.2	36.7 ± 16.5

Mean ± standard deviation (excluding data from patients with a BLQ[a)] value)
a) Below the lower limit of quantitation (<0.1 μg/mL)
b) This value is not a trough concentration.
c) The Q2W group, 12 weeks after switching to subcutaneous tocilizumab 162 mg once weekly
d) The Q2W group, 40 weeks after switching to subcutaneous tocilizumab 162 mg once weekly

6.R Outline of the review conducted by PMDA

6.R.1 Relationship between serum tocilizumab concentration and efficacy

The applicant explained the relationship between serum tocilizumab concentration and the efficacy of subcutaneous tocilizumab 162 mg administered at a reduced dosing interval in patients with RA who had an inadequate response to subcutaneous tocilizumab 162 mg every 2 weeks.

The applicant's explanation:

More than 95% of the soluble IL-6 receptor binds to tocilizumab to form immune complexes while serum tocilizumab trough concentration remains at ≥1 μg/mL (*Blood*. 2008;112:3959-64). In addition, data obtained during the previous development of tocilizumab indicate that serum tocilizumab trough concentration should be maintained at ≥1 μg/mL to normalize CRP and to improve the symptoms/signs of RA (see "Review Report for Actemra 80 mg for Intravenous Infusion, Actemra 200 mg for Intravenous Infusion, and Actemra 400 mg for Intravenous Infusion dated January 22, 2008" and "Review Report for Actemra 162 mg Syringe for SC Injection and Actemra 162 mg Auto-injector for SC Injection dated February 25, 2013").

In Study MRA231JP conducted to develop this new dosage regimen, serum tocilizumab trough concentrations at baseline were 3.81 ± 3.71 μg/mL in the QW group and 2.49 ± 3.48 μg/mL in the Q2W group. These concentrations tended to be lower than the serum tocilizumab trough concentration at Week 12 (9.74 ± 7.18 μg/mL) in Study MRA229JP, a clinical study that demonstrated the efficacy of subcutaneous tocilizumab 162 mg every 2 weeks. Among the patients enrolled in Study MRA231JP, 15 (9 of 21 in the QW group and 6 of 21 in the Q2W group) had a serum tocilizumab trough concentration of ≥1 μg/mL at baseline.

Serum tocilizumab trough concentration at Week 12 in the QW group (19.7 ± 14.3 μg/mL) tended to be higher than that in the Q2W group (Table 1). In addition, the reduced dosing interval of tocilizumab tended to greatly improve "the proportion of patients with CRP ≤0.3 mg/dL" and "the change in DAS28 from baseline," independent of serum tocilizumab trough concentration at baseline (Table 2).

These results indicate that a reduced dosing interval of subcutaneous tocilizumab 162 mg is expected to increase serum tocilizumab trough concentrations, decrease the CRP levels, and improve the clinical symptoms even in patients with a serum tocilizumab trough concentration ≥1 μg/mL if they have an inadequate response to subcutaneous tocilizumab 162 mg every 2 weeks.

Table 2. Proportion of patients with CRP ≤0.3 mg/dL and changes in DAS28 from baseline, by serum tocilizumab trough concentration at baseline (Study MRA231JP)

	Assessment points	Total		Baseline tocilizumab trough concentration <1 μg/mL		Baseline tocilizumab trough concentration ≥1 μg/mL	
		QW	Q2W	QW	Q2W	QW	Q2W
Proportion of patients with CRP ≤0.3 mg/dL[a)]	Baseline	14.3 (3/21)	42.9 (9/21)	8.3 (1/12)	33.3 (5/15)	22.2 (2/9)	66.7 (4/6)
	Week 2	66.7 (14/21)	42.1 (8/19)	58.3 (7/12)	28.6 (4/14)	77.8 (7/9)	80.0 (4/5)
	Week 4	63.2 (12/19)	52.9 (9/17)	54.5 (6/11)	41.7 (5/12)	75.0 (6/8)	80.0 (4/5)
	Week 8	78.9 (15/19)	47.1 (8/17)	72.7 (8/11)	41.7 (5/12)	87.5 (7/8)	60.0 (3/5)
	Week 12	89.5 (17/19)	64.7 (11/17)	90.9 (10/11)	50.0 (6/12)	87.5 (7/8)	100.0 (5/5)
Change in DAS28[b)]	Week 2	−1.23 ± 0.90 (21)	−0.50 ± 0.68 (20)	−0.96 ± 0.80 (12)	−0.72 ± 0.60 (14)	−1.60 ± 0.95 (9)	0.00 ± 0.62 (6)
	Week 4	−1.25 ± 1.25 (21)	−0.44 ± 0.93 (20)	−0.83 ± 1.32 (12)	−0.59 ± 0.94 (14)	−1.82 ± 0.93 (9)	−0.10 ± 0.90 (6)
	Week 8	−1.70 ± 1.50 (21)	−0.83 ± 0.97 (20)	−1.66 ± 1.74 (12)	−1.05 ± 0.98 (14)	−1.76 ± 1.21 (9)	−0.30 ± 0.77 (6)
	Week 12	−2.14 ± 1.71 (21)	−0.84 ± 1.14 (20)	−2.38 ± 1.81 (12)	−1.10 ± 1.21 (14)	−1.83 ± 1.60 (9)	−0.25 ± 0.71 (6)

% (n/N) for proportion of patients with CRP ≤0.3 mg/dL
Mean ± standard deviation (n) for change in DAS28
a) Pharmacokinetic analysis set, OC
b) FAS, LOCF

PMDA's view:

PMDA concluded from the clinical-pharmacological viewpoint that the data submitted indicated that a reduced dosing interval of subcutaneous tocilizumab tended to increase serum tocilizumab trough concentration and improve the clinical symptoms.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the results of a Japanese clinical study in patients with RA (Study MRA231JP, CTD 5.3.5.1-1, -12).

7.1 Phase III study (CTD 5.3.5.1-1, -12: Study MRA231JP [May 2014 to January 2017])

A randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of subcutaneous tocilizumab 162 mg once weekly in patients with RA who had an inadequate response to subcutaneous tocilizumab 162 mg every 2 weeks[1)] (target sample size, 50 patients [25 per group]) [for pharmacokinetics, see Section "6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA"].

[1] Patients who had (1) DAS28 >3.2, (2) ≥4 tender joints + ≥4 swollen joints, and (3) CRP ≥0.3 mg/dL within 2 weeks after the last (≥4th) dose of subcutaneous tocilizumab 162 mg every 2 weeks.

Patients received subcutaneous tocilizumab 162 mg once weekly or every 2 weeks for 12 weeks (the double-blind phase). All patients who completed the double-blind phase rolled over to open-label treatment with subcutaneous tocilizumab 162 mg once weekly for 40 weeks (the open-label phase).

Of the 43 patients randomized with stratification by the DAS28 score at screening (≤5.1 or >5.1) [for the definition of DAS28, see Section "10. Others"], 42 (21 per group) were included in the safety analysis set, excluding 1 who did not receive the study drug. Of the 42 patients, 41 (21 in the QW group and 20 in the Q2W group) were included in the Full Analysis Set (FAS), excluding 1 who did not undergo any post-treatment efficacy assessments. FAS was used for efficacy analyses. During the double-blind phase, 9.5% (2 of 21) of patients in the QW group and 19.0% (4 of 21) of patients in the Q2W group discontinued the study treatment, primarily because of inadequate response (2 in the Q2W group), treatment refusal/poor cooperation (1 in the QW group), death (1 in the QW group), or adverse events (1 in the Q2W group).

In total, 36 patients (19 in the QW group and 17 in the Q2W group) completed the double-blind phase and rolled over to the open-label phase. Of the 36 patients, 8 (22.2%) discontinued the study treatment because of adverse events (4 patients), treatment refusal/poor cooperation (2 patients), death (1 patient), or inadequate response (1 patient).

Table 3 shows the change in DAS28 score from baseline to Week 12, the primary efficacy endpoint. A pair-wise comparison between the Q2W and QW groups revealed a statistically significant difference, demonstrating the superiority of tocilizumab 162 mg once weekly to tocilizumab 162 mg every 2 weeks.

Table 3. Change in DAS28 from baseline to Week 12 (FAS, LOCF)

	QW	Q2W
Baseline	5.91 ± 1.23 (21)	5.49 ± 1.37 (20)
Week 12	3.77 ± 1.62 (21)	4.65 ± 1.81 (20)
Change from baseline	−2.14 ± 1.71 (21)	−0.84 ± 1.14 (20)
Difference from Q2W [95% CI][a)] *P* value[a)]	−1.21 [−2.13, −0.30] *P* = 0.0108	

Mean ± standard deviation (n)
a) Analysis of covariance model using the DAS28 score at screening as an explanatory variable

The incidences of adverse events by Week 12 were 71.4% (15 of 21 patients) in the QW group and 66.7% (14 of 21 patients) in the Q2W group. Adverse events reported in ≥2 patients in either group were nasopharyngitis (14.3% [3 of 21 patients] in the QW group, 9.5% [2 of 21 patients] in the Q2W group), blood triglycerides increased (9.5% [2 of 21 patients] in the QW group, 0% in the Q2W group), and pharyngitis (0% in the QW group, 9.5% [2 of 21 patients] in the Q2W group). One patient in the QW group died (pneumonia/disseminated intravascular coagulation/septic shock), and a causal relationship to the study drug could not be ruled out. Serious adverse events were reported in 1 patient in the QW group (pneumonia/disseminated intravascular coagulation/septic shock) and 1 patient in the Q2W group (lymphoma). For all of the serious adverse events, a causal relationship to the study drug could not be

ruled out. The outcome of the lymphoma in 1 patient was reported as “recovering/resolving.” During the double-blind phase, 1 patient in the QW group (pneumonia/disseminated intravascular coagulation/septic shock) and 1 patient in the Q2W group (dermatitis allergic) discontinued the study treatment due to adverse events.

The incidences of adverse drug reactions were 47.6% (10 of 21 patients) in the QW group and 52.4% (11 of 21 patients) in the Q2W group during the double-blind phase.

During the entire study period, adverse events occurred in 90.5% (38 of 42) of patients (see Table 4 for common adverse events). In addition to the 1 patient who died during the double-blind phase, 1 patient died (aortic rupture) during the open-label phase and a causal relationship to the study drug could not be ruled out. During the entire study period, serious adverse events occurred in 19.0% (8 of 42) of patients: 2 patients in the double-blind phase and 6 patients (cellulitis, epilepsy, aortic rupture, bile duct stone/cholecystitis, colon cancer, and lung neoplasm malignant/coronary artery stenosis in 1 patient each) in the open-label phase. A causal relationship to the study drug was ruled out for the colon cancer, bile duct stone, cholecystitis, coronary artery stenosis, and epilepsy. During the entire study period, 16.7% (7 of 42) of patients discontinued treatment due to adverse events: 2 patients in the double-blind phase and 5 patients (lymphoma, colon cancer, lung neoplasm malignant, rash, and aortic rupture in 1 patient each) in the open-label phase.

Adverse drug reactions occurred in 71.4% (30 of 42) of patients during the entire study period.

Table 4. Adverse events reported in ≥2 patients during the entire study period (safety analysis set)

	Patients treated with subcutaneous tocilizumab (N = 42)		Patients treated with subcutaneous tocilizumab (N = 42)
Nasopharyngitis	9 (21.4)	Blood triglycerides increased	2 (4.8)
Pharyngitis	5 (11.9)	Eosinophil count increased	2 (4.8)
Diarrhoea	4 (9.5)	White blood cell count decreased	2 (4.8)
Abdominal pain upper	3 (7.1)	Procedural pain	2 (4.8)
Influenza	2 (4.8)	Oropharyngeal pain	2 (4.8)
Helicobacter gastritis	2 (4.8)	Back pain	2 (4.8)
Paronychia	2 (4.8)	Osteoarthritis	2 (4.8)
Cellulitis	2 (4.8)	Oedema peripheral	2 (4.8)
Eczema	2 (4.8)	Iron deficiency anaemia	2 (4.8)
Rash	2 (4.8)	Anxiety disorder	2 (4.8)
Blood cholesterol increased	2 (4.8)	Hypertension	2 (4.8)

n (%)

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

The applicant explained the efficacy of subcutaneous tocilizumab 162 mg administered at the reduced dosing intervals in patients with RA who had an inadequate response to subcutaneous tocilizumab 162 mg every 2 weeks.

The applicant's explanation:

Study MRA231JP was conducted in patients with RA who had an inadequate response to subcutaneous tocilizumab 162 mg every 2 weeks. The change in DAS28 from baseline to Week 12, the primary endpoint (Table 3), demonstrated the superiority of the once-weekly dosing over the every-2-weeks dosing. Table 5 shows changes in other key efficacy endpoints [for the definition of each endpoint, see Section "10. Others"]; the once-weekly dosing tended to show a better result than the every-2-weeks dosing at Week 12 in all the endpoints. The change in DAS28 from baseline to Week 52 (40 weeks after switching to the once-weekly dosing in the Q2W group) was −2.93 ± 1.14, indicating that the improvement in DAS28 was maintained with long-term treatment with subcutaneous tocilizumab 162 mg once weekly.

Table 5. Changes in key efficacy endpoints in Study MRA231JP (FAS, LOCF)

	Assessment points	QW	Q2W	Treatment difference [95% CI]
Primary endpoint				
Change in DAS28	Week 2	−1.23 ± 0.90 (21)	−0.50 ± 0.68 (20)	−0.77 [−1.28, −0.25] a)
	Week 4	−1.25 ± 1.25 (21)	−0.44 ± 0.93 (20)	−0.86 [−1.56, −0.15] a)
	Week 12	−2.14 ± 1.71 (21)	−0.84 ± 1.14 (20)	−1.21 [−2.13, −0.30] a) *P* = 0.0108 a)
Secondary endpoints				
Change in CDAI	Week 2	−10.59 ± 9.45 (21)	−4.87 ± 7.08 (20)	−5.49 [−10.87, −0.11] a)
	Week 4	−9.22 ± 13.63 (21)	−3.48 ± 9.92 (20)	−5.99 [−13.70, 1.71] a)
	Week 12	−16.54 ± 16.63 (21)	−8.17 ± 10.87 (20)	−7.26 [−15.93, 1.40] a)
DAS28 remission rate (<2.6)	Week 2	9.5 (2/21)	10.0 (2/20)	−0.2 [−19.4, 19.1] b)
	Week 4	9.5 (2/21)	10.0 (2/20)	−0.2 [−19.4, 19.1] b)
	Week 12	19.0 (4/21)	10.0 (2/20)	9.4 [−12.1, 31.0] b)
CDAI remission rate (≤2.8)	Week 2	0 (0/21)	0 (0/20)	0.0 [−12.5, 12.5] b)
	Week 4	0 (0/21)	0 (0/20)	0.0 [−12.5, 12.5] b)
	Week 12	4.8 (1/21)	0 (0/20)	4.7 [−10.3, 19.7] b)
ACR20 response rate	Week 2	23.8 (5/21)	10.0 (2/20)	13.8 [−8.5, 36.1] b)
	Week 4	28.6 (6/21)	25.0 (5/20)	3.9 [−22.8, 30.6] b)
	Week 12	52.4 (11/21)	20.0 (4/20)	32.5 [4.7, 60.3] b)
ACR50 response rate	Week 2	4.8 (1/21)	5.0 (1/20)	−0.2 [−17.0, 16.6] b)
	Week 4	4.8 (1/21)	10.0 (2/20)	−5.1 [−23.7, 13.6] b)
	Week 12	38.1 (8/21)	15.0 (3/20)	23.4 [−2.6, 49.4] b)
ACR70 response rate	Week 2	0 (0/21)	0 (0/20)	0.0 [−12.5, 12.5] b)
	Week 4	0 (0/21)	0 (0/20)	0.0 [−12.5, 12.5] b)
	Week 12	14.3 (3/21)	15.0 (3/20)	−0.7 [−23.1, 21.8] b)

Mean ± standard deviation (n) for change in DAS28 and CDAI
% (n/N) for DAS28 remission rate, CDAI remission rate, and ACR response rates
a) Analysis of covariance model using the DAS28 score at screening as an explanatory variable
b) Mantel-Haenszel test stratified by the DAS28 score at screening (≤5.1, >5.1)

According to the application data for the initial approval of subcutaneous tocilizumab (see "Review Report for Actemra 162 mg Syringe for SC Injection dated February 25, 2013"), patients with high body

weight or high BMI who received subcutaneous tocilizumab 162 mg every 2 weeks were less likely to achieve a serum tocilizumab trough concentration ≥1 μg/mL than those receiving intravenous tocilizumab. This suggested that subcutaneous tocilizumab may be less effective than intravenous tocilizumab in patients with high body weight or high BMI. PMDA therefore asked the applicant to explain the effects of body weight, BMI, and serum tocilizumab trough concentration on the efficacy of subcutaneous tocilizumab administered at the reduced dosing intervals.

The applicant's explanation:
Table 6 shows the results of subgroup analyses of the primary endpoint in Study MRA231JP, stratified by body weight, BMI, and serum tocilizumab trough concentration at baseline. Although the number of patients included in each subgroup was limited, the analyses revealed that none of these patient characteristics had effects on the efficacy of subcutaneous tocilizumab 162 mg administered at the reduced dosing intervals.

Table 6. Results of subgroup analyses of change in DAS28 from baseline to Week 12 (Study MRA231JP, FAS, LOCF)

Patient characteristics		QW (N = 21)	Q2W (N = 20)
Body weight	<60 kg	−1.83 ± 1.851 (8)	−1.17 ± 1.299 (8)
	≥60 kg	−2.33 ± 1.659 (13)	−0.63 ± 1.019 (12)
BMI	<18.5 kg/m^2	−2.87 (1)	−
	≥18.5 kg/m^2 and <25 kg/m^2	−1.39 ± 1.744 (11)	−1.03 ± 1.281 (9)
	≥25 kg/m^2	−2.97 ± 1.367 (9)	−0.69 ± 1.044 (11)
Serum tocilizumab trough concentration at baseline	<1 μg/mL	−2.38 ± 1.81 (12)	−1.10 ± 1.21 (14)
	≥1 μg/mL	−1.83 ± 1.60 (9)	−0.25 ± 0.71 (6)

Mean ± standard deviation (n)

In Study MRA231JP, subcutaneous tocilizumab 162 mg once weekly was superior to every 2 weeks in the primary endpoint (change in DAS28 from baseline to Week 12), and tended to show better results in secondary endpoints than every 2 weeks. PMDA therefore concluded that a reduction in dosing interval to once weekly is expected to improve the efficacy of tocilizumab in patients with RA who had an inadequate response to subcutaneous tocilizumab 162 mg every 2 weeks.

7.R.2 Safety

The applicant's explanation about the safety of subcutaneous tocilizumab 162 mg administered at the reduced dosing intervals in patients with RA:
In the double-blind phase of Study MRA231JP, the QW and Q2W groups had a similar incidence of adverse events, and no adverse events had a much higher incidence in the QW group than in the Q2W group [see Section 7.1]. The incidences of adverse events of interest were similar in the QW and Q2W groups (Table 7). Further, the QW and Q2W groups showed a similar time course of the following laboratory parameters: total and differential white blood cell count, platelet count, liver function parameters (total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase,

γ-glutamyl transpeptidase, lactate dehydrogenase), lipid parameters (total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride), and autoantibodies (antinuclear antibodies, anti-DNA antibodies).

Table 7. The incidences of adverse events of interest (Study MRA231JP, safety analysis set)

	Double-blind phase		Entire study period
	QW (N = 21)	Q2W (N = 21)	All patients treated once weekly[a] (N = 38)
Total duration of exposure (person-years)	4.53	4.23	28.85
Infections	6 (28.6) 132.42	7 (33.3) 165.59	20 (52.6) 69.31
Serious infections	1 (4.8) 22.07	0	2 (5.3) 6.93
Gastrointestinal perforation and associated disorders	0	0	0
Anaphylaxis	0	0	0
Administration-related systemic reactions	1 (4.8) 22.07	1 (4.8) 23.66	2 (5.3) 6.93
Administration site reactions	0	0	1 (2.6) 3.47
Haemorrhage	1 (4.8) 22.07	1 (4.8) 23.66	4 (10.5) 13.86
Interstitial lung disease	0	0	0
Neutrophil count decreased (CTCAE[b] Grade ≥3)	0	0	0
Platelet count decreased (CTCAE[b] Grade ≥2)	0	0	0
Hepatic disease	0	0	1 (2.6) 3.47
Stroke	0	0	0
Myocardial infarction/acute coronary syndrome	0	0	0
Malignant tumors	0	1 (4.8) 23.66	2 (5.3) 6.93
Demyelinating disease	0	0	0

Upper row, n (%);
Lower row, incidence rate per 100 person-years, adjusted for the total duration of exposure
a) All patients in the QW group in the double-blind phase plus all patients in the Q2W group who rolled over to the open-label phase
b) Common toxicity criteria for adverse events (ver.4)

Table 8 shows a summary of adverse events and the incidences of adverse events of interest, reported by Week 24 in a foreign phase III study in patients with RA who had an inadequate response to disease-modifying antirheumatic drugs (DMARDs) or human tumor necrosis factor (TNF) inhibitors[2] (Study WA22762).[3] Excluding administration site reactions, the safety profile of subcutaneous tocilizumab 162 mg once weekly was similar to that of intravenous tocilizumab 8 mg/kg every 4 weeks.

[2] Patients who had (1) ≥4 swollen joints + ≥4 tender joints and (2) ESR ≥28 mm/h or CRP ≥1 mg/dL, after ≥8-week fixed-dose treatment with at least 1 DMARD (methotrexate, azathioprine, chloroquine, hydroxychloroquine, leflunomide, or sulfasalazine).
[3] A randomized, double-blind, parallel-group study to evaluate the efficacy and safety of subcutaneous tocilizumab 162 mg once weekly versus control (i.e., intravenous tocilizumab 8 mg/kg every 4 weeks).

Table 8. Incidence of adverse events during 24 weeks of treatment with tocilizumab (Study WA22762, safety analysis set)

	Subcutaneous tocilizumab 162 mg once weekly (N = 631)	Intravenous tocilizumab 8 mg/kg every 4 weeks (N = 631)
Summary of adverse events		
All adverse events	481 (76.2)	486 (77.0)
Serious adverse events	29 (4.6)	33 (5.2)
Deaths	0	1 (<1)
Adverse events leading to drug discontinuation	30 (4.8)	41 (6.5)
Adverse drug reactions	305 (48.3)	277 (43.9)
Adverse events of interest		
Infections	227 (36.0)	247 (39.1)
Opportunistic infections	1 (<1)	1 (<1)
Malignant tumors	4 (<1)	2 (<1)
Anaphylaxis	0	0
Hypersensitivity reactions	44 (7.0)	73 (11.6)
Administration site reactions	64 (10.1)	15 (2.4)
Serious hepatic disease	0	1 (<1)
Serious stroke	0	4 (<1)
Serious myocardial infarction	1 (<1)	0
Serious gastrointestinal perforation	0	0
Serious haemorrhage	1 (<1)	4 (<1)
Serious demyelinating disease	0	0

n (%)

As mentioned above, the safety profile of subcutaneous tocilizumab 162 mg once weekly suggests no new concerns, compared with that of subcutaneous tocilizumab 162 mg every 2 weeks or intravenous tocilizumab. Therefore, the risks associated with subcutaneous tocilizumab 162 mg once weekly is be controllable by continuing the safety measures currently taken for subcutaneous tocilizumab 162 mg every 2 weeks.

PMDA's view:

Although the number of patients evaluated in the Japanese clinical study was limited, the safety data of tocilizumab 162 mg once weekly has revealed no new adverse events of clinical concern, compared with the safety data of subcutaneous tocilizumab 162 mg every 2 weeks or intravenous tocilizumab. The safety of subcutaneous tocilizumab 162 mg once weekly can be managed by issuing safety alerts to ensure that attention is paid to known adverse reactions to tocilizumab.

7.R.3 Timing of switching the dosing interval, etc.

The applicant's explanation:

The following findings have suggested that physicians can determine (a) whether to switch to the shorter dosing interval after the completion of 8-week treatment with subcutaneous tocilizumab 162 mg every 2 weeks, and (b) whether to continue the once-weekly dosing after the completion of 12-week treatment with subcutaneous tocilizumab 162 mg once weekly.

- In the Q2W group of Study MRA229JP, the proportion of patients with a serum tocilizumab concentration ≥1 μg/mL (85.8% [145 of 169 patients]) and that of patients with CRP ≤0.3 mg/dL (93.1% [148 of 159 patients]) remained almost constant from Week 8 onward.

- In the Q2W group of Study MRA231JP, the failure rate at Week 12 (based on European League Against Rheumatism [EULAR] response criteria) did not differ greatly according to the duration of prior treatment with subcutaneous tocilizumab every 2 weeks (8 to 10 weeks, or ≥11 weeks).
- In the QW group of Study MRA231JP, the change in DAS28 from baseline and the response rate (based on EULAR response criteria) tended to increase by Week 12, and thereafter the improved condition was maintained according to unblinded assessment.

PMDA's view based on the reviews in Sections 7.R.1 and 7.R.2:
The dosing interval of subcutaneous tocilizumab 162 mg can be reduced to 1 week in patients with an inadequate response to subcutaneous tocilizumab 162 mg every 2 weeks, as proposed by the applicant. However, the applicant should advise healthcare professionals to consider switching to other drugs or therapies, to prevent tocilizumab from being used continuously in patients with RA inadequately responding to tocilizumab at the reduced dosing intervals.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that subcutaneous tocilizumab 162 mg at a reduced dosing interval has efficacy in the treatment of RA with an inadequate response to subcutaneous tocilizumab 162 mg every 2 weeks, and has acceptable safety in view of its benefits. Compared with the approved dosing interval, the reduced dosing interval has caused no new safety concerns; therefore, the current safety measures should be continued.

PMDA has concluded that tocilizumab may be approved if tocilizumab is not considered to have any particular problems based on comments from the Expert Discussion.

10. Others

The following table shows the definitions of the efficacy endpoints used in the Japanese phase III study (Study MRA231JP).

Endpoints	Definition
ACR20, 50, or 70 response rate	The proportion of patients who fulfill all of the following criteria: ・ ≥20%, ≥50%, or ≥70% reduction in tender joint count out of 68 joints ・ ≥20%, ≥50%, or ≥70% reduction in swollen joint count out of 66 joints ・ ≥20%, ≥50%, or ≥70% improvement in 3 of the following measures: ➢ Patient assessment of pain on VAS ➢ Patient global assessment of disease activity on VAS ➢ Physician global assessment of disease activity on VAS ➢ Assessment of daily activity (Japanese version of RA-specific health assessment questionnaire [JHAQ]) ➢ CRP or ESR level
CDAI	An RA disease activity score, calculated by the following formula: CDAI = TJC + SJC + EGA + PGA TJC: Tender joint count (0-28) SJC: Swollen joint count (0-28) EGA: Evaluator's (physician's) global assessment of disease activity on VAS PGA: Patient global assessment of disease activity on VAS
CDAI remission rate (≤2.8)	The proportion of patients with CDAI ≤2.8 at assessment points
DAS28	An RA disease activity score, calculated by the following formula: DAS28 = $0.56\sqrt{\mathrm{TJC}} + 0.28\sqrt{\mathrm{SJC}} + 0.7 \ln \mathrm{ESR} + 0.014 \times \mathrm{GH}$ TJC: Tender joint count (0-28) SJC: Swollen joint count (0-28) ESR: Erythrocyte sedimentation rate GH: Patient global assessment of general health on VAS
DAS28 remission rate (<2.6)	The proportion of patients with DAS28 <2.6 at assessment points

VAS, Visual analog scale

Review Report (2)

May 11, 2017

Product Submitted for Approval

Brand Name	Actemra 162 mg Syringe for SC Injection
	Actemra 162 mg Auto-injector for SC Injection
Non-proprietary Name	Tocilizumab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	August 25, 2016

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy, Safety, and dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusion on the efficacy, safety, and dosage and administration of Actemra 162 mg Syringe for SC Injection and Actemra 162 mg Auto-injector for SC Injection (hereinafter collectively referred to as "tocilizumab"), described in Review Report (1). The expert advisors also offered the following comments:

> In some of the patients responding to the once-weekly dosing, the effects of tocilizumab may be maintained even after the dosing interval is returned to every 2 weeks; therefore, the necessity of continuing the once-weekly dosing should be investigated.

Taking account of comments from the Expert Discussion, PMDA instructed the applicant to promote the proper use of tocilizumab, to ensure that the appropriate dosing interval is selected according to the condition of each patient and that once-weekly treatment is not prolonged unnecessarily. The applicant agreed.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication, and dosage and administration shown below. The re-examination period for the present

application is the remainder of the re-examination period for the initial approval of the product (until March 24, 2019).

Indication

Treatment of rheumatoid arthritis with an inadequate response to existing therapies (including the inhibition of progression of structural joint damage)

Dosage and Administration

The usual adult dosage is 162 mg of Tocilizumab (Genetical Recombination) administered subcutaneously every 2 weeks. The dosing interval may be reduced to a minimum of 1 week in patients with an inadequate response.