Review Report

May 17, 2016

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.

Brand Name	Cyramza Injection 100 mg Cyramza Injection 500 mg
Non-proprietary Name	Ramucirumab (Genetical Recombination) (JAN*)
Applicant	Eli Lilly Japan K.K.
Date of Application	July 23, 2015
Dosage Form/Strength	Injection: Each 10 mL vial contains 100 mg of Ramucirumab (Genetical Recombination). Each 50 mL vial contains 500 mg of Ramucirumab (Genetical Recombination).
Application Classification	Prescription drug; (4) Drug with new indications, (6) Drug with new dosages
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug V

Results of Review

The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the data submitted demonstrate the efficacy of the product in the treatment of patients with unresectable advanced/recurrent non-small cell lung cancer and acceptable safety in view of the benefits indicated by the data submitted, as shown in Attachment.

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. Further investigations are needed through post-marketing surveillance, etc. on hypertension, proteinuria, haemorrhage (pulmonary haemorrhage in particular), infusion reaction, thromboembolism, gastrointestinal perforation, congestive cardiac failure, posterior reversible encephalopathy syndrome, fistula, disturbance of wound healing, liver disorder, and febrile neutropenia.

Indications

Unresectable advanced/recurrent gastric cancer
Unresectable advanced/recurrent non-small cell lung cancer

(Underline denotes additions.)

Dosage and Administration

1. Unresectable advanced/recurrent gastric cancer

The usual adult dosage is 8 mg/kg (body weight) of Ramucirumab (Genetical Recombination) administered as an intravenous infusion over approximately 60 minutes every 2 weeks. The dose may be adjusted according to the condition of the patient.

2. Unresectable advanced/recurrent non-small cell lung cancer

The usual adult dosage is 10 mg/kg (body weight) of Ramucirumab (Genetical Recombination) administered as an intravenous infusion over approximately 60 minutes every 3 weeks, in combination with docetaxel. The dose may be adjusted according to the condition of the patient.

(Underline denotes additions.)

Condition for Approval
The applicant is required to design and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

April 5, 2016

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	Cyramza Injection 100 mg Cyramza Injection 500 mg
Non-proprietary Name	Ramucirumab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of Application	July 23, 2015
Dosage Form/Strength	Injection: Each 10 mL vial contains 100 mg of Ramucirumab (Genetical Recombination). Each 50 mL vial contains 500 mg of Ramucirumab (Genetical Recombination).
Proposed Indications	Unresectable advanced/recurrent gastric cancer Unresectable advanced/recurrent non-small cell lung cancer (Underline denotes additions.)

Proposed Dosage and Administration

1. Unresectable advanced/recurrent gastric cancer

The usual adult dosage is 8 mg/kg (body weight) of Ramucirumab (Genetical Recombination) administered as an intravenous infusion over approximately 60 minutes every 2 weeks. The dose may be adjusted according to the condition of the patient.

2. Unresectable advanced/recurrent non-small cell lung cancer

The usual adult dosage is 10 mg/kg (body weight) of Ramucirumab (Genetical Recombination) administered as an intravenous infusion over approximately 60 minutes every 3 weeks, in combination with docetaxel. The dose may be adjusted according to the condition of the patient.

(Underline denotes additions.)

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List of Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
Bevacizumab	Bevacizumab (genetical recombination)
BQL	Below the quantification limit
$C_{ave,ss}$	Average serum concentration at steady state
CBDCA	Carboplatin
CDDP	Cisplatin
CI	Confidence interval
CLcr	Creatinine clearance
$C_{max,ss}$	Maximum serum concentration at steady state
C_{min}	Minimum serum concentration
$C_{min,1}$	Minimum serum concentration following first dose
$C_{min,ss}$	Minimum serum concentration at steady state
CV%	Percentage coefficient of variation
DC101	Rat antibody against mouse vascular endothelial growth factor receptor-2
DTX	Docetaxel hydrate
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EGFR-TKI	Epidermal growth factor receptor tyrosine kinase inhibitor
ERB	Ethics Review Board
FN	Febrile Neutropenia
GEM	Gemcitabine hydrochloride
G-CSF	Granulocyte-colony stimulating factor
IDMC	Independent data monitoring committee
Ig	Immunoglobulin
IRRC	Independent Response Review Committee
ITT	intent-to-treat
Japanese clinical practice guideline	Clinical practice guidelines for lung cancer based on evidence-based medicine (EBM), edited by the Japan Lung Cancer Society, 2015 edition
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
NCCN Guideline (non-small cell lung cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer
NSCLC	Non-small cell lung cancer
Nude mouse	Athymic mouse
OS	Overall survival
PEM	Pemetrexed sodium hydrate
PFS	Progression-free survival
PK	Pharmacokinetics
Placebo/DTX	Combination of placebo and docetaxel hydrate
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PS	Performance Status
PTX	Paclitaxel
RAINBOW study	Study 14T-IE-JVBE
Ramucirumab	Ramucirumab (genetical recombination)
Ramucirumab/DTX	Combination of ramucirumab and docetaxel hydrate
Ramucirumab/PTX	Combination of ramucirumab and paclitaxel
REVEL study	Study I4T-MC-JVBA
TE-ADA	Treatment emergent anti-drug antibody
ULN	Upper limit of normal

VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
V_1	Central volume of distribution
V_2	Peripheral volume of distribution

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

1.1 Overview of the product submitted for approval

Ramucirumab (genetical recombination) (hereinafter referred to as "ramucirumab") is a human immunoglobulin G1 (IgG1) monoclonal antibody against human vascular endothelial growth factor (VEGF) receptor 2 (VEGFR-2). It was developed by ImClone Systems Incorporated. Ramucirumab binds to VEGFR-2 to block the binding of the VEGF to VEGFR-2, thereby inhibiting the angiogenesis mediated through VEGFR-2 signaling pathway, leading to the inhibition of tumor growth.

In Japan, ramucirumab was approved in March 2015 for the indication for the treatment of "unresectable advanced/recurrent gastric cancer."

1.2 Development history, etc.

Outside Japan, ImClone Systems initially undertook the clinical development of ramucirumab for non-small cell lung cancer (NSCLC) and initiated a phase II study (Study I4T-IE-JVBJ) involving chemotherapy-naïve patients with stage IIIB or IV NSCLC in January 2009. After that, Eli Lilly and Company (United States) took over the clinical development program. In December 2010, Eli Lilly started a phase III study (REVEL study [14T-MC-JVBA]) involving patients with advanced/recurrent NSCLC with disease progression after first-line platinum-based chemotherapy.

In the US and the European Union, a marketing application for ramucirumab (Cyramza) was submitted for the indication for NSCLC in June 2014 and in February 2015, respectively, with the results of the pivotal REVEL study. Cyramza was approved in the US in December 2014 for the following indication: "CYRAMZA, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA." In the EU, it was approved in January 2016 for the following indication: "Cyramza in combination with docetaxel is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with disease progression after platinum-based chemotherapy."

As of February 2016, Cyramza has been approved in 5 countries or regions for the indication for NSCLC.

In Japan, the applicant started a phase II study (JVCG study) in December 2012, involving patients with advanced/recurrent NSCLC with disease progression after first-line platinum-based chemotherapy.

Recently, a partial change application was submitted for the addition of a new indication (NSCLC) and the dosage and administration for this indication, based on the results of the pivotal REVEL and JVCG studies.

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

Because the present application is intended for addition of the new indication and new dosage, data relating to quality were omitted.

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

3.1 Primary pharmacodynamics

Because ramucirumab does not bind to murine VEGFR-2 (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza Injection 500 mg"), DC101, a rat anti-murine VEGFR-2 antibody, was used in studies to investigate the tumor growth-inhibitory effect in mice. In this section, the dose of docetaxel hydrate (DTX) is expressed on the anhydrous basis.

3.1.1 Effect on tumor vessels (CTD 4.2.1.1.1)

DC101-induced inhibition of angiogenesis was investigated in nude mice with subcutaneously transplanted human NSCLC-derived cell line, HCC827. When the tumor volume reached approximately 620 mm^3, animals were randomized to receive DC101 (6 or 20 mg/kg) intraperitoneally 3 times weekly. The number of microvessels per unit area in tumor tissue slice at 10 days post-randomization was calculated by immunohistochemical staining for murine endothelial cell-specific antigen Meca 32. The

number of microvessels decreased statistically significantly in the DC101 group as compared with the control (rat IgG 20 mg/kg) group ($P < 0.05$, Tukey rank test).

3.1.2 Growth-inhibitory effect on malignant tumor-derived cell lines

3.1.2.1 Growth-inhibitory effect on human NSCLC-derived cell lines (CTD 4.2.1.1.1, 4.2.1.1.2, 4.2.1.1.3, 4.2.1.1.4, 4.2.1.1.5, 4.2.1.1.6, 4.2.1.1.7, 4.2.1.1.8, 4.2.1.1.9, and 4.2.1.1.10)

The tumor growth-inhibitory effect of DC101 was investigated in nude mice with subcutaneously transplanted HCC827 cells. When the tumor volume reached approximately 440 mm^3, animals were randomized to receive DC101 (2, 6, 20, 40, or 60 mg/kg) intraperitoneally 3 times weekly for the first 27 days post-randomization, and tumor volume was calculated. Tumor growth inhibition was statistically significant in the DC101 (6, 20, 40, and 60 mg/kg) groups as compared with the control (rat IgG 60 mg/kg + human IgG 0.6 mg/kg) group ($P = 0.001$, 0.003, 0.0002, and 0.002, respectively; repeated-measures analysis of variance). Also using nude mice with subcutaneously transplanted human NSCLC-derived NCI-H441, NCI-H460, NCI-H292, NCI-H2122, or NCI-H1975 cells, the tumor growth-inhibitory effect of DC101 was investigated in a similar manner. Tumor growth was inhibited statistically significantly in the DC101 group as compared with the control group for all cell lines tested.

The tumor growth-inhibitory effect of DC101 in combination with DTX was investigated in nude mice with transplanted NCI-H1975 cells. For 3 weeks starting at 16 days post-transplantation (mean tumor volume, 150 mm^3), animals intraperitoneally received (a) DC101 (5 or 20 mg/kg twice weekly) alone, (b) DTX (10 mg/kg once weekly) alone, or (c) DC101 (5 or 20 mg/kg twice weekly) in combination with DTX (10 mg/kg once weekly), and tumor volume was calculated. Tumor growth was inhibited statistically significantly in the DC101 (5 or 20 mg/kg) alone group and DTX alone group as compared with the control (rat IgG 20 mg/kg) group ($P = 0.009$ [DC101, 5 mg/kg], $P < 0.001$ [DC101, 20 mg/kg], $P < 0.001$ [DTX]; two-way repeated-measures analysis of variance). Statistically significant inhibition of tumor growth was observed in the groups of animals receiving DC101 (5 or 20 mg/kg) plus DTX as compared with the control group ($P < 0.001$ in both groups; two-way repeated-measures analysis of variance). In contrast, DC101 (20 mg/kg) plus DTX did not inhibit tumor growth statistically significantly as compared with DC101 (20 mg/kg) or DTX alone.

3.R Outline of the review conducted by PMDA

PMDA's view:

The data submitted in support of the initial application has demonstrated the growth-inhibitory activity of ramucirumab against malignant tumor (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza Injection 500 mg"). In addition, the data submitted for the present application support the efficacy of ramucirumab in the treatment of NSCLC.

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

The non-clinical pharmacokinetic data were evaluated in support of the initial application for ramucirumab. The evaluated data were considered applicable to the present application for the new indication and dosage. Therefore, no additional data were submitted under this section.

5. Toxicology and Outline of the Review Conducted by PMDA

The present application is intended for addition of the new indication and dosage. No additional toxicity data were submitted.

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

The results of biopharmaceutic studies and associated analytical methods were evaluated in support of the initial application for ramucirumab. The results were considered applicable to the present application for the new indication and new dosage. Therefore, no additional data were submitted under this section.

6.1 Clinical pharmacology

The pharmacokinetics (PK) of ramucirumab in patients with malignant tumor was investigated after the administration of ramucirumab alone or in combination with an antineoplastic drug (e.g., DTX).

6.1.1 Japanese phase II study (CTD 5.3.5.1.2, Study JVCG [ongoing since December 2012 (data cut-off; December ■, 2014)])

A double-blind, randomized, comparative study was conducted to investigate the PK, etc. of ramucirumab in 197 patients with advanced/recurrent NSCLC with disease progression after first-line platinum-based chemotherapy (98 in the ramucirumab/DTX group, 99 in the placebo/DTX group) (94 patients evaluable for PK analysis). The patients received intravenously ramucirumab (10 mg/kg) or placebo in combination with DTX (60 mg/m^2) every 3 weeks, and their serum ramucirumab concentrations and plasma DTX concentrations were determined.

Table 1 shows the time-course change in serum ramucirumab concentrations. The results suggested that the concentration reaches steady state before the dose in Cycle 5. The time-course change in plasma DTX concentrations was similar between the ramucirumab/DTX group and the placebo/DTX group. In the ramucirumab/DTX group, anti-ramucirumab antibody levels were measured in 87 patients after the start of treatment. Of these, 2 patients (2.3%) were positive for the antibody, and they were both positive for treatment emergent anti-drug antibodies (TE-ADA).[1)] No neutralizing antibody was detected in any of the samples tested.

Table 1. Serum ramucirumab concentrations in subjects receiving multiple doses of ramucirumab at 10 mg/kg (μg/mL)

Cycle	Pre-dose		1 hour post-dose	
	n	Serum ramucirumab concentration	n	Serum ramucirumab concentration
1	-	-	76	217 (29)
2	55	18.0 (59)	64	219 (27)
3	52	30.1 (44)	-	-
4	31	32.5 (41)	30	225 (19)
5	30	39.9 (52)	-	-
6	15	35.5 (44)	-	-

Geometric mean (CV%); -, not determined

6.1.2 Foreign phase III study (CTD 5.3.5.1.1, REVEL study [ongoing since December 2010 (data cut-off; December ■, 2013)])

A double-blind, randomized, comparative study was conducted to investigate the efficacy and safety of ramucirumab in 1253 patients with advanced/recurrent NSCLC with disease progression after first-line platinum-based chemotherapy (628 in the ramucirumab/DTX group, 625 in the placebo/DTX group) (594 patients included in the PK analysis). The patients received intravenously ramucirumab (10 mg/kg) or placebo in combination with DTX (75 mg/m^2) every 3 weeks, and their serum ramucirumab concentrations were determined.

The geometric mean (percentage coefficient of variation [CV%]) serum ramucirumab concentration before the administration of ramucirumab in Cycles 3 and 5 was 28.3 μg/mL (65%) and 38.4 μg/mL (63%), respectively. In the ramucirumab/DTX group, anti-ramucirumab antibody levels were measured in 506 patients after the start of treatment. Of those, 28 patients (5.5%) were positive for the antibody. Of the 28 patients, 9 (1.8%) were TE-ADA-positive. One patient (0.2%) was neutralizing antibody-positive.

6.1.3 Pharmacokinetic interactions between ramucirumab and DTX

The applicant's explanation:

The following findings suggest that combination therapy of ramucirumab with DTX is unlikely to cause pharmacokinetic interactions:

- In the foreign phase II study (Study I4T-IE-JVCC), no clear difference was observed in the PK of DTX between DTX alone and ramucirumab plus DTX (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza Injection 500 mg").

1) Defined as a >4-fold rise in antibody titer from baseline, or an antibody titer of >1:20 for patients who were negative for anti-ramucirumab antibodies at baseline or whose baseline data were missing (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza 500 mg").

- In the Japanese phase II study (JVCG study), the time-course change in plasma DTX concentrations was similar between the ramucirumab/DTX group and the placebo/DTX group [see "6.1.1 Japanese phase II study"].
- Table 2 shows the PK parameters in patients who received a single dose of ramucirumab (10 mg/kg) in combination with DTX in the foreign phase II study (Study I4T-IE-JVCC) and the Japanese phase I study (Study I4T-IE-JVBX) and in those who received a single dose of ramucirumab (8 mg/kg) in the foreign phase II study (Study I4T-IE-JVCA) and the Japanese phase II study (Study I4T-JE-JVCL). The PK parameters of ramucirumab were generally similar with and without coadminstration of DTX. Also, the exposure to ramucirumab tended to increase dose-proportionally at ≥8 mg/kg (see "Review Report dated February 16, 2015: Cyramza Injection100 mg, Cyramza Injection 500 mg").

Table 2. PK parameters of ramucirumab administered with or without concomitant DTX

	Study	With or without concomitant DTX	Ramucirumab dose (mg/kg)	n	C_{max}[*1] (μg/mL/mg)	AUC_{inf}[*1] (μg·day/mL/mg)	CL (mL/h)	V_{ss} (L)
Non-Japanese	I4T-IE-JVCC	With	10	18	0.365 (34)	2.26 (29)[*2]	18.4 (29)[*2]	3.47 (43)[*2]
	I4T-IE-JVCA	Without	8	16	0.358 (18)	2.88 (29)[*3]	18.1 (27)[*3]	3.95 (23)[*3]
Japanese	I4T-IE-JVBX	With	10	7	0.472 (20)	3.07 (24)	13.6 (24)	2.96 (32)
	I4T-JE-JVCL	Without	8	6	0.431 (14)	2.79 (20)[*4]	15.0 (20)[*4]	3.29 (27)[*4]

Geometric mean (CV%); [*1] dose-normalized PK parameters; [*2] n = 11; [*3] n = 15; [*4] n = 3

6.1.4 PPK analysis

6.1.4.1 JVBA-PPK analysis

A population pharmacokinetics (PPK) analysis was performed using a non-linear mixed effect model (software NONMEM ver.7.2), based on the PK data (896 patients, 3908 time points) obtained from the following 9 studies: Japanese phase I studies (Studies I4T-IE-JVBW, I4T-IE-JVBX, and I4T-IE-JVBY), a global phase III study (RAINBOW study), foreign phase II studies (Studies I4T-IE-JVBJ, I4T-IE-JVCA, and I4T-IE-JVCC), and foreign phase III studies (REVEL study and Study I4T-IE-JVBD). The PK of ramucirumab was described by a 2-compartment model that included the zero order absorption process and the first order elimination processes.

Possible covariates for CL, V_1, and V_2 of ramucirumab were age, body weight, sex, race, ethnicity, renal function,[2)] serum albumin, hepatic function,[3)] cancer type, and dose. CLcr, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin were also evaluated as possible covariates for the CL of ramucirumab.

Cancer type was selected as a significant covariate for V_2. The analysis revealed prolonged $t_{1/2}$ in patients with NSCLC (22.6 days) as compared with patients with other types of cancers (13.3 days). However, no clear difference was observed in the estimated CL between patients with NSCLC and patients with other types of cancers (0.0149 and 0.0142 L/h, respectively), which suggested that the exposure at steady state is similar between the patient groups.

6.1.4.2 JVCG-PPK analysis

PK data (91 patients, 880 time points) obtained from the Japanese phase II study (Study JVCG) were combined with the PK data used for the JVBA-PPK analysis and those (1639 patients, 6427 time points) obtained from 2 global phase III studies (Studies I4T-MC-JVBB and I4T-IE-JVBF). A PPK analysis was then performed on the combined data using a non-linear mixed effect model (software NONMEM ver.7.3). The PK of ramucirumab was described by a 2-compartment model that included the zero order absorption process and the first order elimination processes. Race (Japanese or non-Japanese) was evaluated as a possible covariate for CL, V_1, and V_2 of ramucirumab.

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2) Patients with normal renal function (CLcr ≥ 90 mL/min), patients with mild renal impairment (60 mL/min ≤ CLcr <90 mL/min), patients with moderate renal impairment (30 mL/min ≤ CLcr <60 mL/min), and patients with severe renal impairment (15 mL/min ≤ CLcr <30 mL/min)

3) Patients with normal hepatic function (total bilirubin ≤ upper limit of normal [ULN] and AST ≤ ULN), patients with mild hepatic impairment (total bilirubin ≤1.5 × ULN and AST > ULN, or ULN < total bilirubin ≤1.5 × ULN), and patients with moderate hepatic impairment (1.5 × ULN < total bilirubin ≤ 3 × ULN)

As a result, race was not selected as a significant covariate for CL, V_1, or V_2 of ramucirumab.

6.1.5 Difference in the PK of ramucirumab between Japanese and non-Japanese patients

The applicant's explanation:

The following findings indicate no clear difference in the PK of ramucirumab between Japanese and non-Japanese patients:

- In the Japanese phase II study (JVCG study) and the foreign phase III study (REVEL study), multiple doses of ramucirumab (10 mg/kg) were administered in combination with DTX. The trough serum concentration of ramucirumab was similar in both studies [see "6.1.1 Japanese phase II study" and "6.1.2 Foreign phase III study"].
- In the PPK analysis, race was not selected as a significant covariate for any PK parameter of ramucirumab [see "6.1.4.2 JVCG-PPK analysis"].

6.1.6 Relationship between exposure and efficacy or safety

6.1.6.1 Relationship between exposure and efficacy

The results of the REVEL study were analyzed to investigate a relationship between exposure to ramucirumab[4] ($C_{min,1}$, $C_{min,ss}$, $C_{max,ss}$, and $C_{ave,ss}$) and overall survival (OS) or progression-free survival (PFS). A correlation was observed between increased exposure ($C_{min,1}$, $C_{min,ss}$, $C_{max,ss}$, and $C_{ave,ss}$) and prolonged OS or PFS).

6.1.6.2 Relationship between exposure and safety

The results of the REVEL study were analyzed to assess the relationship between exposure to ramucirumab[4] ($C_{min,1}$, $C_{min,ss}$, $C_{max,ss}$, and $C_{ave,ss}$) and Grade ≥3 febrile neutropenia (FN), neutropenia, hypertension, or fatigue. These events were Grade ≥3 adverse events occurring in ≥5% of patients in the ramucirumab/DTX group and with an incidence >2% higher than in the placebo/DTX group. A correlation was observed between increased exposure ($C_{min,1}$, $C_{min,ss}$, $C_{max,ss}$, and $C_{ave,ss}$) and increased incidences of Grade ≥3 FN and hypertension.

6.R Outline of the review conducted by PMDA

6.R.1 Effect of anti-ramucirumab antibody on the PK of ramucirumab

The applicant's explanation on the expression of anti-ramucirumab antibody and its effect on the PK of ramucirumab:

The expression of anti-ramucirumab antibody was investigated based on the results of the following studies: 4 Japanese phase I studies (Studies I4T-IE-JVBI, I4T-IE-JVBW, I4T-IE-JVBX, and I4T-IE-JVBY), 1 Japanese phase II study (Study JVCG), 2 foreign phase I studies (Studies I4T-IE-JVBM and I4T-IE-JVBN), 11 foreign phase II studies (Studies I4T-IE-JVBK, I4T-IE-JVBP, I4T-IE-JVBQ, I4T-IE-JVBR, I4T-IE-JVBH, I4T-IE-JVBJ, I4T-IE-JVBO, I4T-IE-JVBS, I4Y-IE-JCDB, I4T-IE-JVBL, and I4T-IE-JVCC), 3 foreign phase III studies (Study I4T-IE-JVBD, REVEL study, and Study I4T-IE-JVBC), and 3 global phase III studies (RAINBOW study, Study I4T-MC-JVBB, and Study I4T-IE-JVBF). Anti-ramucirumab antibodies were detected in 145 of 2977 patients (4.9%) from whom a blood sample was collected at least once after the start of treatment. Of those, 88 patients (3.0%) were TE-ADA-positive, and 14 patients (0.5%) were neutralizing antibody-positive. No clear difference was observed in the expression of anti-ramucirumab antibody between the overall NSCLC patient population or patients treated intravenously with ramucirumab (10 mg/kg) in combination with DTX every 3 weeks and all patients who underwent anti-ramucirumab antibody testing.

The effect of the anti-ramucirumab antibody on the PK of ramucirumab was investigated in the REVEL study and Study I4T-IE-JVBC. In both studies, ramucirumab was administered according to the proposed dosage regimen, and anti-ramucirumab antibodies were detected during the pre-determined treatment period. Table 3 shows the range of serum ramucirumab concentrations at the time points when anti-ramucirumab antibody levels were measured. In both studies, serum ramucirumab concentrations in anti-ramucirumab antibody-positive patients at the time points when they tested positive for the antibody were within the range of serum ramucirumab concentrations in antibody-negative patients at the time points when they were tested.

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[4] Individual values were estimated using JVBA-PPK analysis [see "6.1.4.1 JVBA-PPK analysis"].

Table 3. Range of serum ramucirumab concentrations (μg/mL) following multiple doses of ramucirumab (10 mg/kg)

Study	Cycle	Anti-ramucirumab antibody-positive patients		Anti-ramucirumab antibody-negative patients	
		n	C_{min}	n	C_{min}
REVEL	3	4	BQL*-23.3	294	BQL*-107.6
	5	4	24.8-45.8	184	BQL*-128.0
	9	1	3.9	18	20.0-97.9
I4T-IE-JVBC	3	2	BQL,* BQL*	444	BQL*-131.0
	5	2	49.8, 78.0	360	BQL*-404.0

Min. to Max (individual values when n = 1 or 2); * <1.9 or <2.5 μg/mL (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza Injection 500 mg")

The small number of patients investigated precludes a definitive conclusion on the effect of anti-ramucirumab antibody on the PK of ramucirumab. Nevertheless, the anti-ramucirumab antibody is considered to have no clear effect on the PK of ramucirumab.

PMDA's view:
The submitted data do not show any clear effect of anti-ramucirumab antibody on the PK of ramucirumab. However, because of limited relevant study data, further data should be collected to investigate the effect of anti-ramucirumab antibody on the PK of ramucirumab. Any new findings should be appropriately communicated to healthcare professionals.

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

The applicant submitted efficacy and safety evaluation data from 3 clinical studies (1 Japanese phase I study, 1 Japanese phase II study, and 1 foreign phase III study) as listed in Table 4. The applicant also submitted reference data from 6 clinical studies (4 foreign phase II studies, 1 foreign phase III study, and 1 global phase III study). Data from the Japanese phase I study (Study I4T-IE-JVBX), foreign phase II studies (Studies I4T-IE-JVCC and I4T-IE-JVBJ), foreign phase III study (Study I4T-IE-JVBC), and global phase III study (RAINBOW study) had already been submitted in support of the initial application and are therefore omitted in this report (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza Injection 500 mg").

Table 4. List of clinical studies on efficacy and safety

Data category	Region	Study	Phase	Eligible patients	Number of treated patients	Dosing regimen	Main endpoints
Evaluation	Japan	I4T-JE-JVCG	II	Patients with advanced/recurrent NSCLC with disease progression after first-line platinum-based chemotherapy	192 (a) 94 (b) 98	(a) Ramucirumab 10 mg/kg plus DTX 60 mg/m^2 or (b) placebo plus DTX 60 mg/m^2 administered intravenously every 3 weeks.	Efficacy Safety
	Foreign	I4T-MC-JVBA (REVEL)	III	Patients with advanced/recurrent NSCLC with disease progression after first-line platinum-based chemotherapy	1253 (a) 628 (b) 625	(a) Ramucirumab 10 mg/kg plus DTX 75 mg/m^2 or (b) placebo plus DTX 75 mg/m^2 administered intravenously every 3 weeks.	Efficacy Safety
Reference	Foreign	I4T-IE-JVBL	II	Chemotherapy-naïve patients with advanced (stage IV) NSCLC	280	Group A: Combination of PEM with CBDCA or CDDP[*1] Group B: Ramucirumab 10 mg/kg in combination with PEM and CBDCA or CDDP,[*1] administered intravenously every 3 weeks Group C: Combination of GEM with CBDCA or CDDP[*2] Group D: Ramucirumab 10 mg/kg in combination with GEM and CBDCA or CDDP,[*2] administered intravenously every 3 weeks	Safety
		I5B-IE-JGDE	II	Patients with recurrent/refractory glioblastoma multiforme	80 (a) 40 (b) 40	(a) Ramucirumab 8 mg/kg administered intravenously every 2 weeks (b) Olaratumab (unapproved in Japan) 20 mg/kg administered intravenously every 2 weeks.	Safety

[*1] PEM (500 mg/m^2) and CBDCA (dose equivalent to AUC 6 mg·mL/min) or CDDP (75 mg/m^2) were administered intravenously on Day 1 of every 3-week cycle.
[*2] GEM (1000 mg/m^2) was administered intravenously on Days 1 and 8 and CBDCA (dose equivalent to AUC 5 mg·mL/min) or CDDP (75 mg/m^2) were administered intravenously on Day 1 of every 3-week cycle.

Each clinical study is outlined below. Major adverse events other than death observed in each clinical study are described in "7.3 Adverse events, etc. observed in clinical studies."

7.1 Evaluation data

7.1.1 Japanese clinical study

7.1.1.1 Japanese phase II study (CTD 5.3.5.1.2, Study JVCG [ongoing since December 2012 (data cut-off; December [redacted], 2014)])

A double-blind, randomized, comparative study in patients with advanced/recurrent NSCLC with disease progression after first-line platinum-based chemotherapy (target sample size; 154 patients without a history of monotherapy with an epidermal growth factor receptor tyrosine kinase inhibitor [EGFR-TKI], 40 patients with a history of EGFR-TKI monotherapy) was conducted at 28 medical centers in Japan to evaluate the efficacy and safety of ramucirumab/DTX versus placebo/DTX.

The patients received intravenously ramucirumab (10 mg/kg) or placebo every 3 weeks in combination with intravenous DTX (60 mg/m^2) every 3 weeks, until any of the treatment discontinuation criteria was met.

Of 197 patients enrolled and randomized (98 in the ramucirumab/DTX group, 99 in the placebo/DTX group), 192 patients (94 in the ramucirumab/DTX group, 98 in the placebo/DTX group) were included in the safety analysis, except 5 patients (4 in the ramucirumab/DTX group, 1 in the placebo/DTX group) who did not receive the study drug. Of the 192 patients included in the safety analysis, 157 patients (76 in the ramucirumab/DTX group, 81 in the placebo/DTX group) without a history of EGFR-TKI monotherapy were the primary population for efficacy analyses. The patient population was the same as that of the foreign phase III study (REVEL study).

The primary efficacy endpoint of the study was investigator-assessed PFS in the primary population. The results are shown in Table 5 and the Kaplan-Meier curves of PFS are presented in Figure 1.

Table 5. Results of PFS analysis
(assessed by the investigator; primary population; data cut-off, December [redacted], 2014)

	Ramucirumab/DTX	Placebo/DTX
Number of patients	76	81
Number of events (%)	63 (82.9)	72 (88.9)
Median (95% CI) (months)	5.22 (3.52, 6.97)	4.21 (2.83, 5.62)
Hazard ratio (95% CI)[*1]	0.83 (0.59, 1.16)	
P value (two-sided)[*2]	0.504	

[*1] Cox proportional hazards model adjusted for stratification factors (ECOG PS [0 vs. 1], sex [male vs. female], previous maintenance therapy [with vs. without]); [*2] Stratified log-rank test (stratified by ECOG PS [0 vs. 1], sex [male vs. female], and previous maintenance therapy [with vs. without])

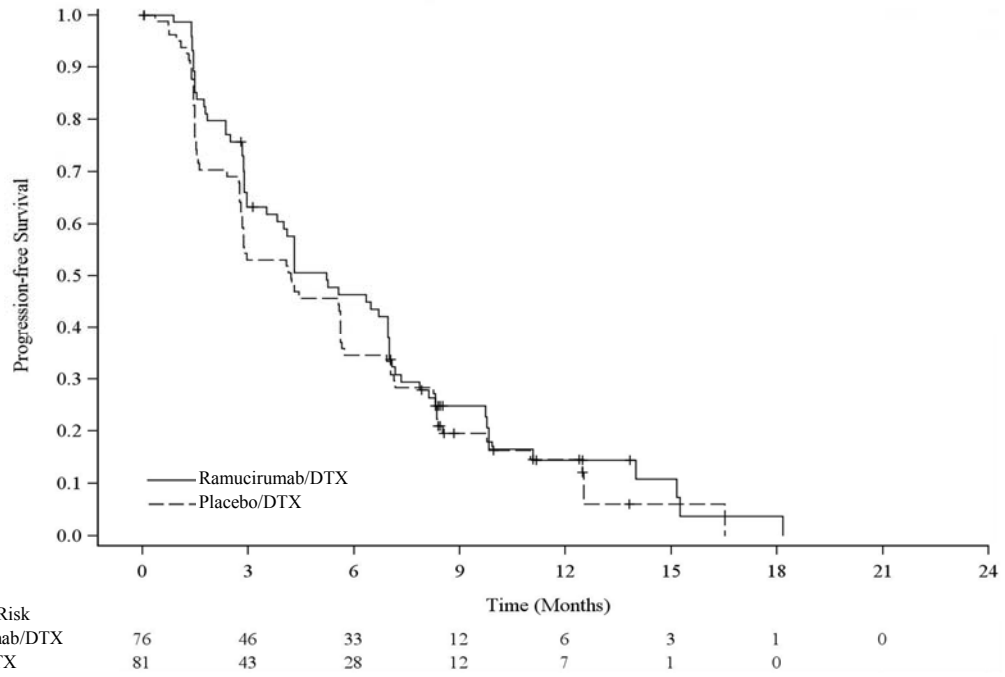

Figure 1. Kaplan-Meier curves of PFS in the primary analysis
(assessed by the investigator; primary population; data cut off, December [redacted], 2014)

The safety analysis revealed deaths of 2 of 94 patients (2.1%) in the ramucirumab/DTX group and 3 of 98 patients (3.1%) in the placebo/DTX group during the treatment period or within 30 days after the last dose of the study drug. The cause of death other than disease progression (2 patients in the ramucirumab/DTX group, 2 patients in the placebo/DTX group) was septic shock in 1 patient in the placebo/DTX group. A causal relationship to the study drug could not be ruled out for septic shock

7.1.2 Foreign clinical study

7.1.2.1 Foreign phase III study (CTD 5.3.5.1.1, REVEL study [ongoing since December 2010 (data cut off; December ■, 2013)])

A double-blind, randomized, comparative study in patients with advanced/recurrent NSCLC with disease progression after first-line platinum-based chemotherapy[5)] (target sample size, 1242 patients) was conducted at 216 medical centers overseas to evaluate the efficacy and safety of ramucirumab/DTX versus placebo/DTX.

The patients received intravenously ramucirumab (10 mg/kg) or placebo every 3 weeks in combination with intravenous DTX (75 mg/m^2) every 3 weeks, until any of the criteria for treatment discontinuation was met. However, the independent data monitoring committee (IDMC) recommended the use of the reduced starting dose of DTX in patients enrolled in East Asia (South Korea and Taiwan). This was because of decreased neutrophil count and FN reported more frequently in the region than in other regions.[6)] In response to the recommendation, the clinical study protocol was revised in May 2012 so as to use the starting dose of DTX 60 mg/m^2 for patients enrolled in East Asia.

A total of 1253 patients were enrolled and randomized (628 in the ramucirumab/DTX group, 625 in the placebo/DTX group). All the patients randomized were included in the intent-to-treat (ITT) population and the efficacy analysis was based on the ITT population. Among the patients in the ITT population, 1245 patients were included in the safety analysis, except 8 patients (4 in the ramucirumab/DTX group and 4 in the placebo/DTX group) who did not receive the study drug. During the study, 3 patients assigned to the placebo/DTX group received ramucirumab by mistake. The patients were therefore included in the ramucirumab/DTX group (patients evaluable for safety: 627 in the ramucirumab/DTX group, 618 in the placebo/DTX group).

The primary endpoint was OS. The results are shown in Table 6 and the Kaplan-Meier curves of OS are presented in Figure 2. One of the study sites submitted unmasked safety data of 9 patients to the Ethics Review Board (ERB) by a method considered a protocol deviation. The unmasked safety data was consequently passed to the relevant monitors and clinical trial coordinators, who were supposed to be blinded to the data. After the exclusion of the 9 patients (2 in the ramucirumab/DTX group, 7 in the placebo/DTX group), the median OS (95% CI) of 626 patients in the ramucirumab/DTX group and 618 in the placebo/DTX group was 10.5 (9.5, 11.2) months and 9.1 (8.3, 9.9) months, respectively, with a hazard ratio (95% CI) of 0.852 (0.745, 0.973). The results were similar to those obtained before the exclusion of the 9 patients.

Table 6. Results of OS analysis (ITT population; data cut-off, December ■, 2013)

	Ramucirumab/DTX	Placebo/DTX
Number of patients	628	625
Number of death (%)	428 (68.2)	456 (73.0)
Median (95% CI) (months)	10.5 (9.5, 11.2)	9.1 (8.4, 10.0)
Hazard ratio (95% CI)[*1]	0.857 (0.751, 0.979)	
P value (two-sided)[*2]	0.024	

[*1] Cox proportional hazards model adjusted for stratification factors (ECOG PS [0, 1], sex [male, female], previous maintenance therapy [with, without], region [East Asia, other]).

[*2] Stratified log-rank test (stratified by ECOG PS [0 vs. 1], sex [male vs. female], previous maintenance therapy [with vs. without], and region [East Asia vs. other]), significance level of 0.05 (two-sided)

5) Patients with a history of chemotherapy with ≥2 regimens were excluded from the study, and patients with a history of EGFR-TKI monotherapy were therefore not included.

6) The relevant adverse events reported by the time of issuance of the IDMC recommendation were summarized by patients enrolled in East Asia or other regions. The results for East Asia and other regions are as follows: neutrophil count decreased in 28 of 57 patients (49.1%) and 64 of 483 patients (13.3%), respectively; FN in 14 of 57 patients (24.6%) and 61 of 483 patients (12.6%), respectively; serious neutropenia in 6 of 57 patients (10.5%) and 22 of 483 patients (4.6%), respectively; serious FN in 14 of 57 patients (24.6%) and 48 of 483 patients (9.9%), respectively; neutropenia leading to dose reduction of DTX in 7 of 57 patients (12.3%) and 39 of 483 patients (8.1%), respectively; and FN leading to dose reduction of DTX in 7 of 57 patients (12.3%) and 27 of 483 patients (5.6%), respectively.

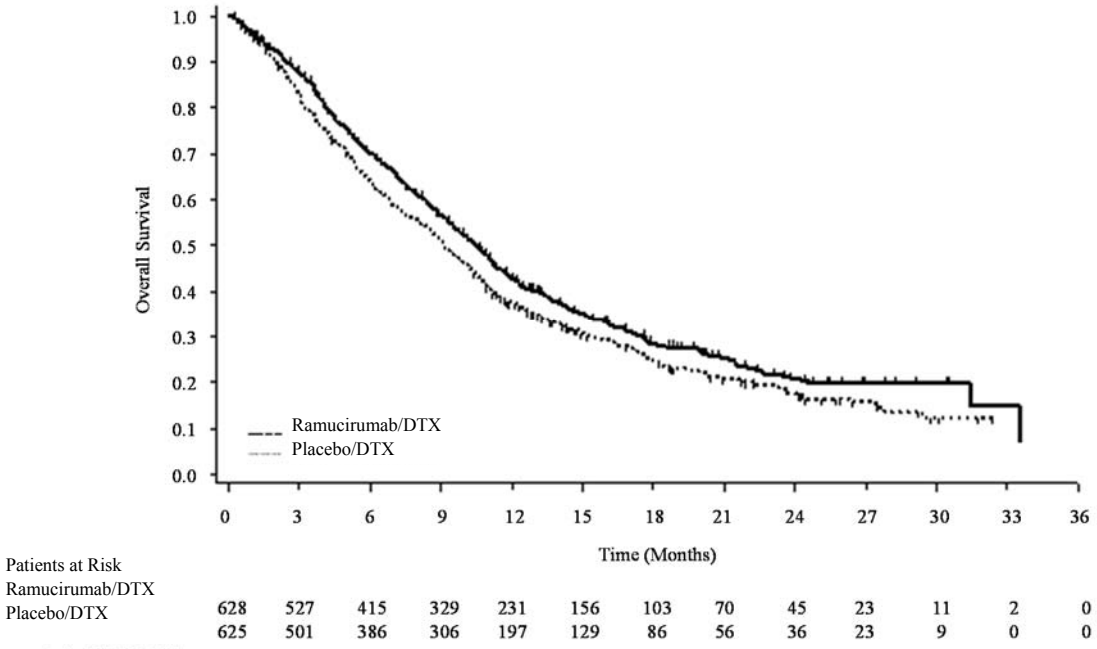

Figure 2. Kaplan-Meier curves of OS in the primary analysis (ITT population; data cut off, December [redacted], 2013)

The safety analysis revealed deaths of 53 of 627 patients (8.5%) in the ramucirumab/DTX group and in 58 of 618 patients (9.4%) in the placebo/DTX group during the treatment period or within 30 days after the last dose of the study drug. The causes of deaths other than disease progression (22 of 627 patients in the ramucirumab/DTX group, 23 of 618 patients in the placebo/DTX group) were summarized by treatment group. In the ramucirumab/DTX group, death and pulmonary haemorrhage in 4 patients each, acute respiratory distress syndrome, cardiac arrest, cardio-respiratory arrest, haemoptysis, lung infection, pulmonary embolism, and respiratory failure in 2 patients each, and pneumonia, bronchopneumonia, cachexia, gastrointestinal haemorrhage, metastatic neoplasm, neutropenic sepsis, pneumonitis, sepsis, and *Stenotrophomonas* sepsis in 1 patient each; and, in the placebo/DTX group, respiratory failure in 5 patients, pneumonia in 3 patients, death, pulmonary haemorrhage, acute respiratory distress syndrome, haemoptysis, and septic shock in 2 patients each, cardiac arrest, cardio-respiratory arrest, sepsis, acute respiratory failure, aortic aneurysm rupture, hepatic failure, ischaemic stroke, lobar pneumonia, pneumonia aspiration, respiratory acidosis, respiratory arrest, respiratory distress, respiratory tract haemorrhage, sudden death, superior vena cava syndrome, supraventricular tachycardia, and upper gastrointestinal haemorrhage in 1 patient each. A causal relationship to the study drug could not be ruled out for pulmonary haemorrhage and cardiac arrest in 2 patients each, and pneumonia, acute respiratory distress syndrome, haemoptysis, pulmonary embolism, bronchopneumonia, gastrointestinal haemorrhage, pneumonitis, and sepsis in 1 patient each in the ramucirumab/DTX group; and respiratory failure, pneumonia, pulmonary haemorrhage, cardio-respiratory arrest, sepsis, ischaemic stroke, respiratory tract haemorrhage, supraventricular tachycardia, and upper gastrointestinal haemorrhage in 1 patient each in the placebo/DTX group.

7.2 Reference data

7.2.1 Foreign clinical studies

7.2.1.1 Foreign phase II study (CTD 5.3.5.1.3, Study I4T-IE-JVBL [ongoing since October 2010 (data cut-off; [redacted], 20[redacted])])

An open-label, randomized, comparative study in chemotherapy-naïve patients with advanced (Stage IV) NSCLC (target sample size: 140 patients with nonsquamous NSCLC, 140 patients with squamous NSCLC)[7)] was conducted at 41 medical centers overseas to evaluate the efficacy and safety of ramucirumab in combination with the conventional chemotherapy (pemetrexed sodium hydrate [PEM] and a platinum-based antineoplastic drug in patients with non-squamous NSCLC, gemcitabine

7) Because the study in patients with squamous NSCLC is ongoing, only data of patients with nonsquamous NSCLC were submitted.

hydrochloride [GEM] and a platinum-based antineoplastic drug in patients with squamous NSCLC) as compared with the conventional chemotherapy alone.

A total of 140 patients with nonsquamous NSCLC were enrolled in this study and randomized to Group A (PEM + platinum-based antineoplastic drug group) or Group B (ramucirumab + PEM + platinum-based antineoplastic drug group) (71 in Group A and 69 in Group B). Of the 140 randomized patients, 136 patients (69 in Group A and 67 in Group B) were treated with the study drug and were included in the safety analysis.

The safety analysis revealed deaths of 7 of 69 patients (10.1%) in Group A and 4 of 67 patients (6.0%) in Group B during the treatment period or within 30 days after the last dose of the study drug. The causes of deaths other than disease progression (3 of 69 patients in Group A, 1 of 67 patients in Group B) were myocardial infarction, cardio-respiratory arrest, embolism, and respiratory failure in 1 patient each in Group A; and multi-organ failure, myocardial infarction, and sudden death in 1 patient each in Group B. A causal relationship to the study drug could not be ruled out for myocardial infarction and sudden death in 1 patient each in Group B.

7.2.1.2 Foreign phase II study (CTD 5.3.5.2.2, Study I5B-IE-JGDE [[redacted] to [redacted]])

An open-label, randomized, comparative study in patients with recurrent or refractory glioblastoma multiforme (target sample size, 80 patients) was conducted at 11 medical centers overseas to evaluate the efficacy and safety of ramucirumab versus olaratumab (unapproved in Japan).

All 80 patients enrolled and randomized (40 in the ramucirumab group, 40 in the olaratumab group) were treated with the study drug and were included in the safety analysis.

The safely analysis revealed a death of 1 of 40 patients (2.5%) in the ramucirumab group during the treatment period or within 30 days after the last dose of the study drug. The cause of death was neoplasm progression, and its causal relationship to ramucirumab was ruled out.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA reviewed the present application for ramucirumab primarily based on the foreign phase III study (REVEL study) enrolling patients with advanced/recurrent NSCLC with disease progression after first-line platinum-based chemotherapy. This was because the REVEL study was considered the pivotal study for evaluation of the efficacy and safety of ramucirumab. The efficacy and safety of ramucirumab in Japanese patients was evaluated mainly based on the results of the Japanese phase II study (JVCG study).

7.R.2 Efficacy

PMDA's conclusion:

The efficacy of ramucirumab has been demonstrated in patients with advanced/recurrent NSCLC with disease progression after first-line platinum-based chemotherapy. The following sections show the details of the reviews.

7.R.2.1 Setting of control group

The applicant's justification for the control group used in the REVEL and JVCG studies:

When the REVEL study was planned in 2010, DTX was known to improve OS in patients with advanced/recurrent NSCLC with disease progression after first-line platinum-based chemotherapy *(J Clin Oncol.* 2000;18:2095-103, *J Clin Oncol.* 2000;18:2354-62). At that time, the US National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer (NCCN Guideline [non-small cell lung cancer]) (v.1. 2010) recommended DTX for the relevant patient population.

In Japan, when the JVCG study was planned in 2012, DTX was also recommended for the relevant patient population in the Japanese clinical practice guideline (2012).

Accordingly, the use of a control group with placebo/DTX was appropriate in both studies.

PMDA accepted the applicant's explanation.

7.R.2.2 Endpoints and evaluation results

PMDA's view:

Treatment of patients with advanced/recurrent NSCLC with disease progression after first-line platinum-based chemotherapy is intended to improve survival. OS was therefore the appropriate primary endpoint of the REVEL study.

The REVEL study demonstrated the superiority of ramucirumab/DTX to placebo/DTX in OS [see "7.1.2.1 Foreign phase III study"]. Ramucirumab/DTX was shown to be effective in the patients eligible for enrollment in the REVEL study.

7.R.2.3 Efficacy in Japanese patients

The applicant's explanation on the efficacy of ramucirumab in Japanese patients:

The primary endpoint of the JVCG study was the investigator-assessed PFS in the primary population. The analysis of the PFS results revealed that the point estimate of the hazard ratio calculated by the Cox proportional hazards model adjusted for stratification factors (Eastern Cooperative Oncology Group Performance Status [ECOG PS], sex, and previous maintenance therapy) was >1 [see "7.1.1.1 Japanese phase II study"]. Table 7 shows the results of PFS adjudicated by the Independent Response Review Committee (IRRC), which was a sensitivity analysis.

Table 7. Results of PFS analysis (assessed by IRRC; primary population; data cut off, December [redacted], 2014)

	Ramucirumab/DTX	Placebo/DTX
Number of patients	76	81
Number of events (%)	59 (77.6)	70 (86.4)
Median (95% CI) (months)	5.75 (4.30, 7.29)	4.07 (2.83, 5.62)
Hazard ratio (95% CI)[*1]	0.70 (0.50, 1.00)	
P value (two-sided)[*2]	0.081	

[*1] Cox proportional hazards model adjusted for stratification factors (ECOG PS [0 vs. 1], sex [male vs. female], previous maintenance therapy [with vs. without]); [*2] Stratified log-rank test (stratified by ECOG PS [0 vs. 1], sex [male vs. female], and previous maintenance therapy [with vs. without])

The secondary endpoints of the JVCG study were (a) OS and (b) response rate in the primary population. The secondary endpoints of the REVEL study were (c) PFS and (d) response rate. The results are as follows:

(a) The median OS (95% confident interval [CI]) was 15.15 (12.58, not estimable) months in the ramucirumab/DTX group and 13.93 (11.43, not estimable) months in the placebo/DTX group. The Cox proportional hazards ratio (95% CI) adjusted for stratification factors (ECOG PS [0 vs. 1], sex [male vs. female], previous maintenance therapy [with vs. without]) was 0.77 (0.48, 1.24).

(b) The investigator-assessed response rate was 28.9% (22 of 76 patients) in the ramucirumab/DTX group and 18.5% (15 of 81 patients) in the placebo/DTX group.

(c) The median investigator-assessed PFS (95% CI) was 4.5 (4.2, 5.3) months in the ramucirumab/DTX group and 3.0 (2.8, 3.9) months in the placebo/DTX group. The Cox proportional hazards ratio (95% CI) adjusted for stratification factors (ECOG PS [0 vs. 1], sex [male vs. female], previous maintenance therapy [with vs. without], region [East Asia vs. other]) was 0.76 (0.68, 0.86).

(d) The investigator-assessed response rate was 22.9% (144 of 628 patients) in the ramucirumab/DTX group and 13.6% (85 of 625 patients) in the placebo/DTX group.

Of note, the starting dose of DTX in both ramucirumab/DTX and placebo/DTX groups of the REVEL study was 75 mg/m^2, whereas the starting dose of DTX in the JVCG study was determined as 60 mg/m^2 recommended by the Japanese clinical practice guideline (2012) for the second-line therapy for NSCLC. Although the starting dose of DTX differed between the 2 studies, the efficacy of ramucirumab, as demonstrated in the REVEL study, is expected in Japanese patients as well, because of the following findings:

- The PK of ramucirumab was similar between Japanese and non-Japanese patients [see "6.1.5 Difference in PK of ramucirumab between Japanese and non-Japanese patients"].
- No drug-drug interactions were observed between ramucirumab and DTX [see "6.1.3 Pharmacokinetic interactions between ramucirumab and DTX"].
- The median OS and other parameters were similar between Japanese patients with NSCLC on DTX (60 mg/m^2) monotherapy and non-Japanese patients with NSCLC on DTX (75 mg/m^2) monotherapy (e.g., *Cancer Chemother Pharmacol*. 2001;48:356-60).
- The results of efficacy outcome measures in the JVCG study were similar to those in the REVEL study.

PMDA's view:
The applicant's explanation is generally acceptable. As explained, ramucirumab is expected to be effective in Japanese patients with advanced/recurrent NSCLC with disease progression after first-line platinum-based chemotherapy. However, because of the lack of data on the safety of ramucirumab in combination with DTX (75 mg/m^2) in Japanese patients with NSCLC, the fact that the different starting doses of DTX were used in the REVEL and JVCG studies should be appropriately communicated to healthcare professionals through the package insert or by other means [see "7.R.5.1 Dosage and administration"].

7.R.3 Safety [see "7.3 Adverse events, etc. observed in clinical studies" for adverse events]

PMDA's conclusions:
As shown in the reviews in the sections below, the use of ramucirumab in patients with advanced/recurrent NSCLC requires close attention to FN and pulmonary haemorrhage as well as the adverse events of special interest identified in the review of the initial application (hypertension, proteinuria, haemorrhage, infusion-related reaction, thromboembolism, gastrointestinal perforation, cardiac failure congestive, neutropenia/leukopenia, posterior reversible encephalopathy syndrome, fistula, disturbance of wound healing, and liver disorder) (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza Injection 500 mg"). Patients on treatment with ramucirumab should be carefully monitored for these adverse events.

Despite these adverse events requiring close attention, ramucirumab is well tolerated in patients with NSCLC when the patients are followed by physicians with adequate knowledge of and experience with cancer chemotherapy, through monitoring and controlling of adverse events as well as appropriate measures including dose reduction, or interruption or discontinuation of ramucirumab.

7.R.3.1 Safety profile of ramucirumab and difference in safety profile between Japanese and non-Japanese patients

The applicant assessed the safety profile of ramucirumab based on the safety data obtained from the JVCG study in Japanese patients and the REVEL study in non-Japanese patients and provided the following explanation.

Table 8 outlines safety results of the JVCG and REVEL studies.

Table 8. Outline of safety (JVCG and REVEL studies)

	Number of patients (%)			
	JVCG study (Japanese)		REVEL study (Non-Japanese)	
	Ramucirumab/DTX (N = 94)	Placebo/DTX (N = 98)	Ramucirumab/DTX (N = 627)	Placebo/DTX (N = 618)
All adverse events	94 (100)	98 (100)	613 (97.8)	594 (96.1)
Grade ≥3 adverse events	89 (94.7)	93 (94.9)	495 (78.9)	444 (71.8)
Adverse events resulting in death	1 (1.1)	1 (1.0)	34 (5.4)	35 (5.7)
Serious adverse events	28 (29.8)	31 (31.6)	269 (42.9)	262 (42.4)
Adverse events leading to treatment discontinuation	51 (54.3)	29 (29.6)	132 (21.1)	83 (13.4)
Adverse events leading to interruption	3 (3.2)	0	8 (1.3)	7 (1.1)
Adverse events leading to dose reduction	53 (56.4)	37 (37.8)	180 (28.7)	130 (21.0)

In the JVCG study, adverse events of any grade with an incidence ≥10% higher in the ramucirumab/DTX group than in the placebo/DTX group were stomatitis (51 of 94 patients [54.3%] in the ramucirumab/DTX group vs. 31 of 98 patients [31.6%] in the placebo/DTX group), epistaxis (45 of 94 patients [47.9%] vs. 18 of 98 patients [18.4%]), FN (32 of 94 patients [34.0%] vs. 18 of 98 patients [18.4%]), proteinuria (27 of 94 patients [28.7%] vs. 8 of 98 patients [8.2%]), platelet count decreased (22 of 94 patients [23.4%] vs. 13 of 98 patients [13.3%]), AST increased (19 of 94 patients [20.2%] vs. 7 of 98 patients [7.1%]), ALT increased (15 of 94 patients [16.0%] vs. 3 of 98 patients [3.1%]), and hypertension (10 of 94 patients [10.6%] vs. 0 patients). Grade ≥3 adverse events with an incidence ≥5% higher in the former than in the latter were neutrophil count decreased (69 of 94 patients [73.4%] vs. 63 of 98 patients [64.3%]), white blood cell count decreased (60 of 94 patients [63.8%] vs. 54 of 98 patients [55.1%]), FN (32 of 94 patients [34.0%] vs. 18 of 98 patients [18.4%]), and stomatitis (6 of 94 patients [6.4%] vs. 1 of 98 patients [1.0%]). Serious adverse events with an incidence ≥2% higher in the former than in the latter were FN (8 of 94 patients [8.5%] vs. 6 of 98 patients [6.1%]), decreased appetite (4 of 94 patients [4.3%] vs. 1 of 98 patients [1.0%]), and general physical health deterioration (2 of 94 patients [2.1%] vs. 0 patients). Adverse events leading to treatment discontinuation with an incidence ≥2% higher in the former than in the latter were neutrophil count decreased (9 of 94 patients [9.6%] vs. 2 of 98 patients [2.0%]), malaise (4 of 94 patients [4.3%] vs. 0 patients), hypoalbuminaemia (3 of 94 patients [3.2%] vs. 1 of 98 patients [1.0%]), anaemia (2 of 94 patients [2.1%] vs. 0 patients), and proteinuria (2 of 94 patients [2.1%] vs. 0 patients).

In the REVEL study, adverse events of any grade with an incidence ≥10% higher in the ramucirumab/DTX group than in the placebo/DTX group were stomatitis (146 of 627 patients [23.3%] in the ramucirumab/DTX group vs. 80 of 618 patients [12.9%] in the placebo/DTX group) and epistaxis (116 of 627 patients [18.5%] vs. 40 of 618 patients [6.5%]). Grade ≥3 adverse events with an incidence ≥5% higher in the former than in the latter were neutropenia (219 of 627 patients [34.9%] vs. 173 of 618 patients [28.0%]) and FN (100 of 627 patients [15.9%] vs. 62 of 618 patients [10.0%]). A serious adverse event with an incidence ≥2% higher in the former than in the latter was FN (86 of 627 patients [13.7%] vs. 51 of 618 patients [8.3%]). There were no adverse events leading to treatment discontinuation with an incidence ≥2% higher in the ramucirumab/DTX group than in the placebo/PDX group.

The applicant's explanation on the difference in the safety profile of ramucirumab between Japanese and non-Japanese patients:
In the ramucirumab/DTX group, adverse events of any grade with an incidence ≥20% higher in Japanese patients than in non-Japanese patients were neutrophil count decreased (73 of 94 patients [77.7%] in the Japanese subgroup vs. 113 of 627 patients [18.0%] in the non-Japanese subgroup), white blood cell count decreased (73 of 94 patients [77.7%] vs. 58 of 627 patients [9.3%]), alopecia (63 of 94 patients [67.0%] vs. 162 of 627 patients [25.8%]), decreased appetite (58 of 94 patients [61.7%] vs. 182 of 627 patients [29.0%]), stomatitis (51 of 94 patients [54.3%] vs. 146 of 627 patients [23.3%]), epistaxis (45 of 94 patients [47.9%] vs. 116 of 627 patients [18.5%]), malaise (44 of 94 patients [46.8%] vs. 9 of 627 patients [1.4%]), proteinuria (27 of 94 patients [28.7%] vs. 21 of 627 patients [3.3%]), and hypoalbuminaemia (28 of 94 patients [29.8%] vs. 25 of 627 patients [4.0%]). Grade ≥3 adverse events

with an incidence ≥10% higher in the former than in the latter were neutrophil count decreased (69 of 94 patients [73.4%] vs. 97 of 627 patients [15.5%]), white blood cell count decreased (60 of 94 patients [63.8%] vs. 36 of 627 patients [5.7%]), and FN (32 of 94 patients [34.0%] vs. 100 of 627 patients [15.9%]). An adverse event leading to treatment discontinuation with an incidence ≥5% higher in the former than in the latter was neutrophil count decreased (9 of 94 patients [9.6%] vs. 0 patients). In the ramucirumab/DTX group, there were no serious adverse events with an incidence ≥5% higher in the Japanese patients than in non-Japanese patients.

Decreased appetite, alopecia, and malaise occurred more frequently in Japanese patients than in non-Japanese patients, but their incidences in Japanese patients were similar between the ramucirumab/DTX group and the placebo/DTX group. Neutrophil count decreased, white blood cell count decreased, and FN were observed more frequently in Japanese patients than in non-Japanese patients of the placebo/DTX group as well. Therefore, the higher incidences of these events in Japanese patients are attributable to concomitant DTX. Most cases of stomatitis, epistaxis, hypoalbuminaemia, and proteinuria in Japanese patients were Grade ≤2 and controllable, and therefore ramucirumab/DTX should be well tolerated by Japanese patients.

The applicant added the following explanation on the difference in the safety profile of ramucirumab between patients with unresectable advanced/recurrent NSCLC (JVCG and REVEL studies) and patients with unresectable advanced/recurrent gastric cancer (RAINBOW study) as the approved indication:

Table 9 outlines the safety of ramucirumab in the JVCG, REVEL, and RAINBOW studies.

Table 9. Outline of safety (JVCG, REVEL, and RAINBOW studies)

	Number of patients (%)					
	JVCG		REVEL		RAINBOW	
	Ramucirumab/ DTX (N = 94)	Placebo/ DTX (N = 98)	Ramucirumab/ DTX (N = 627)	Placebo/ DTX (N = 618)	Ramucirumab/ PTX(N = 327)	Placebo/ PTX (N = 329)
All adverse events	94 (100)	98 (100)	613 (97.8)	594 (96.1)	324 (99.1)	322 (97.9)
Grade ≥3 adverse events	89 (94.7)	93 (94.9)	495 (78.9)	444 (71.8)	267 (81.7)	206 (62.6)
Adverse events resulting in death	1 (1.1)	1 (1.0)	34 (5.4)	35 (5.7)	39 (11.9)	51 (15.5)
Serious adverse events	28 (29.8)	31 (31.6)	269 (42.9)	262 (42.4)	153 (46.8)	139 (42.2)
Adverse events leading to treatment discontinuation	51 (54.3)	29 (29.6)	132 (21.1)	83 (13.4)	102 (31.2)	80 (24.3)

The incidence of Grade ≥3 FN was ≥10% higher in patients receiving ramucirumab and DTX in the REVEL and JVCG studies than those receiving ramucirumab and paclitaxel (PTX) in the RAINBOW study (32 of 94 patients [34.0%] in the ramucirumab/DTX group of the JVCG study, 100 of 627 patients [15.9%] in the ramucirumab/DTX group of the REVEL study, 10 of 327 patients [3.1%] in the ramucirumab/PTX group of the RAINBOW study, respectively). The same was true of neutrophil count decreased (69 of 94 patients [73.4%], 97 of 627 patients [15.5%], 1 of 327 patients [0.3%]). The incidence of serious FN was ≥5% higher in the ramucirumab/DTX group of the REVEL and JVCG studies than in the ramucirumab/PTX group of the RAINBOW study (8 of 94 patients [8.5%], 86 of 627 patients [13.7%], 8 of 327 patients [2.4%]).

PMDA's view:
In the JVCG and REVEL studies, some adverse events occurred more frequently in the ramucirumab/DTX group than in the placebo/DTX group. However, the observed adverse events were mostly known to be induced by the concomitant drugs, and most of the events occurring more frequently in the ramucirumab/DTX group than in the placebo/DTX group were Grade ≤2. Taking account of these findings, ramucirumab/DTX should be well tolerated by patients with NSCLC when the patients are followed by a physician with adequate knowledge of and experience with cancer chemotherapy, through monitoring and controlling of adverse events as well as appropriate measures including treatment interruption.

The limited experiences with the use of ramucirumab in Japanese patients with NSCLC preclude an accurate comparison of the safety of ramucirumab between Japanese and non-Japanese patients. Nevertheless, considering that no fatal or serious adverse events tended to occur more frequently in Japanese patients than in non-Japanese patients, ramucirumab/DTX will be well tolerated also in Japanese patients when they are followed by a physician with adequate knowledge of and experience with cancer chemotherapy, through appropriate measures including treatment interruption, dose reduction, or treatment discontinuation. However, Grade ≥3 neutrophil count decreased and FN occurred more frequently in Japanese patients than in non-Japanese patients, in the ramucirumab/DTX group of Japanese patients than in the placebo/DTX group of Japanese patients, and, in patients with NSCLC than in patients with gastric cancer (approved indication). Therefore, the use of ramucirumab in patients with NSCLC requires close attention to neutrophil count decreased and FN.

The occurrence of the above adverse events in the JVCG and REVEL studies should be appropriately communicated to healthcare professionals through written materials.

The following sections explain FN and pulmonary haemorrhage. Serious FN occurred more frequently in patients with NSCLC than in patients with gastric cancer. Pulmonary haemorrhage is a characteristic symptom of NSCLC. The package insert of bevacizumab (genetical recombination), another angiogenesis inhibitor like ramucirumab, also includes precautionary advice on pulmonary haemorrhage in the "Clinically Significant Adverse Reactions" section.

7.R.3.2 FN

The applicant's explanation on ramucirumab-induced FN:
An FN-related adverse event tabulated by MedDRA (MedDRA/J [Medical Dictionary for Regulatory Activities Japanese version] ver17.1 in the JVCG study, MedDRA/J ver16.1 in the REVEL study) preferred term (PT) was febrile neutropenia. Table 10 shows the incidences of FN in the JVCG and REVEL studies.

Table 10. Incidences of FN (JVCG and REVEL studies)

	Number of patients (%)			
	JVCG (Japanese)		REVEL (non-Japanese)	
	Ramucirumab/DTX (N = 94)	Placebo/DTX (N = 98)	Ramucirumab/DTX (N = 627)	Placebo/DTX (N = 618)
All adverse events	32 (34.0)	18 (18.4)	100 (15.9)	62 (10.0)
Grade ≥3 adverse events	32 (34.0)	18 (18.4)	100 (15.9)	62 (10.0)
Adverse events resulting in death	0	0	0	0
Serious adverse events	8 (8.5)	6 (6.1)	86 (13.7)	51 (8.3)
Adverse events leading to treatment discontinuation	4 (4.3)	4 (4.1)	3 (0.5)	3 (0.5)
Adverse events leading to interruption	0	0	0	0
Adverse events leading to dose reduction	24 (25.5)	15 (15.3)	41 (6.5)	28 (4.5)

The median (range) time to onset of FN in the ramucirumab/DTX group was 10.5 (7-320) days in the JVCG study and 11.5 (6-234) days in the REVEL study.

In the REVEL study, the following possible risk factors for FN in the ramucirumab/DTX group were investigated: age (≥65 years vs. <65 years), ECOG PS (0 vs. 1), history of treatment with taxanes, and history of radiation therapy. The incidence of FN tended to be higher in patients aged ≥65 years (odds ratio [95% CI] of FN in patients aged ≥65 years to patients aged <65 years, 1.528 [1.092, 2.139]).

In both JVCG and REVEL studies, the use of granulocyte-colony stimulating factor (G-CSF) was permitted for supportive therapy. However, neither study protocol required that G-CSF be administered for the purpose of prevention of FN without decreased neutrophil count or pyrexia being observed (primary G-CSF prophylaxis).

Prophylactic use of G-CSF[8)] was performed in 6 of 94 patients (6.4%) in the ramucirumab/DTX group and in 2 of 98 patients (2.0%) in the placebo/DTX group in the JVCG study, and in 162 of 627 patients (25.8%) in the ramucirumab/DTX group and in 150 of 618 patients (24.3%) in the placebo/DTX group in the REVEL study.

The applicant's explanation on the measures taken for ramucirumab-induced FN:
The US NCCN Guideline (2015), the Japanese clinical practice guideline (Guideline for Proper Use of G-CSF, Japan Society of Clinical Oncology, 2013 [Kanehara & Co., Ltd]), etc. recommend the primary prophylaxis of FN with G-CSF if the incidence of chemotherapy-induced FN is ≥20%. Because the incidence of FN in the ramucirumab/DTX group was 34.0% in the JVCG study, the primary prophylaxis with G-CSF should be considered based on these guidelines. The incidence of FN in the JVCG study will be communicated to healthcare professionals using the package insert. Countermeasures for FN will also be included in written materials.

PMDA's view:
Patients with NSCLC on treatment with ramucirumab should be carefully monitored for FN because (i) the incidence of the event was higher in the ramucirumab/DTX group than in the placebo/DTX group in both JVCG and REVEL studies, (ii) the incidence of FN in those who received ramucirumab/DTX was higher in Japanese patients than in non-Japanese patients, and (iii) the incidence of FN was also higher in patients with NSCLC than patients with gastric cancer (approved indication). The occurrence of FN in the clinical studies should be appropriately communicated to healthcare professionals for precautions using the package insert.

Given that the incidence of FN in the JVCG study in Japanese patients was 34.0% (32 of 94 patients), the following advice should be appropriately given to healthcare professionals in the package insert: (a) appropriate use of G-CSF, including primary prophylaxis, should be considered in patients with NSCLC receiving ramucirumab in combination with DTX, by referring to the latest clinical practice guideline, etc., and (b) appropriate measures should be taken if FN occurs.

7.R.3.3 Pulmonary haemorrhage

The applicant's explanation on ramucirumab-associated pulmonary haemorrhage:
Pulmonary haemorrhage-related adverse events tabulated by MedDRA PT were as follows: bronchial haemorrhage, haemoptysis, haemothorax, laryngeal haematoma, laryngeal haemorrhage, pleural haemorrhage, pulmonary alveolar haemorrhage, pulmonary contusion, pulmonary haematoma, pulmonary haemorrhage, respiratory tract haemorrhage, respiratory tract haemorrhage neonatal, thoracic haemorrhage, and tracheal haemorrhage.

Table 11 summarizes the incidences of pulmonary haemorrhage-related adverse events in the JVCG and REVEL studies. Table 12 shows pulmonary haemorrhage-related adverse events by PT.

Table 11. Summary of pulmonary haemorrhage-related adverse events (JVCG and REVEL studies)

	Number of patients (%)			
	JVCG (Japanese)		REVEL (non-Japanese)	
	Ramucirumab/DTX (N = 94)	Placebo/DTX (N = 98)	Ramucirumab/DTX (N = 627)	Placebo/DTX (N = 618)
All adverse events	9 (9.6)	6 (6.1)	49 (7.8)	46 (7.4)
Grade ≥3 adverse events	1 (1.1)	0	8 (1.3)	8 (1.3)
Adverse events resulting in death	0	0	6 (1.0)	6 (1.0)
Serious adverse events	1 (1.1)	0	9 (1.4)	9 (1.5)
Adverse events leading to treatment discontinuation	1 (1.1)	0	0	0
Adverse events leading to interruption	0	0	0	2 (0.3)
Adverse events leading to dose reduction	0	0	0	0

8) Prophylactic administration of G-CSF for the primary prevention was not tabulated separately from that for other purpose.

Table 12. Pulmonary haemorrhage-related adverse events (JVCG and REVEL studies)

Preferred term*	Number of patients (%)							
	JVCG (Japanese)				REVEL (non-Japanese)			
	Ramucirumab/DTX (N = 94)		Placebo/DTX (N = 98)		Ramucirumab/DTX (N = 627)		Placebo/DTX (N = 618)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Haemoptysis	6 (6.4)	0	6 (6.1)	0	36 (5.7)	4 (0.6)	32 (5.2)	4 (0.6)
Pulmonary haemorrhage	3 (3.2)	1 (1.1)	0	0	13 (2.1)	4 (0.6)	10 (1.6)	3 (0.5)
Laryngeal haemorrhage	0	0	0	0	3 (0.5)	0	4 (0.6)	0
Respiratory tract haemorrhage	0	0	0	0	0	0	1 (0.2)	1 (0.2)

* MedDRA/J ver17.1 in the JVCG study, MedDRA/J ver16.1 in the REVEL study

In the JVCG study, a serious adverse event related to pulmonary haemorrhage was observed in 1 of 94 patients (1.1%, pulmonary haemorrhage) in the ramucirumab/DTX group. Its causal relationship to the study drug could not be ruled out.

In the REVEL study, serious adverse events related to pulmonary haemorrhage were observed in 9 of 627 patients (1.4%; haemoptysis in 6 patients, pulmonary haemorrhage in 4 patients [some patients had >1 event]) in the ramucirumab/DTX group, and in 9 of 618 patients (1.5%; haemoptysis and pulmonary haemorrhage in 4 patients each, respiratory tract haemorrhage in 1 patient) in the placebo/DTX group. A causal relationship to the study drug could not be ruled out for haemoptysis in 5 patients and pulmonary haemorrhage in 2 patients in the ramucirumab/DTX group and haemoptysis in 2 patients and pulmonary haemorrhage and respiratory tract haemorrhage in 1 patient each in the placebo/DTX group. Serious adverse events related to pulmonary haemorrhage with a fatal outcome were pulmonary haemorrhage in 4 patients and haemoptysis in 2 patients in the ramucirumab/DTX group and pulmonary haemorrhage in 3 patients, haemoptysis in 2 patients, and respiratory tract haemorrhage in 1 patient in the placebo/DTX group. A causal relationship to the study drug could not be ruled out for pulmonary haemorrhage in 2 patients and haemoptysis in 1 patient in the ramucirumab/DTX group and pulmonary haemorrhage and respiratory tract haemorrhage in 1 patient each in the placebo/DTX group.

The median time to onset (range) of pulmonary haemorrhage in the ramucirumab/DTX group was 16 (1-169) days in the JVCG study and 51 (6-269) days in the REVEL study.

Bevacizumab, an angiogenesis inhibitor like ramucirumab, is not indicated for squamous NSCLC because of its risk of pulmonary haemorrhage. PMDA asked the applicant to explain the occurrence of pulmonary haemorrhage by histology of NSCLC.

The applicant's explanation:
In the JVCG study, pulmonary haemorrhage-related adverse events were observed in none of 9 patients with squamous NSCLC in the ramucirumab/DTX group and 1 of 10 patients with squamous NSCLC (10%, haemoptysis) in the placebo/DTX group; and in 9 of 85 patients (10.6%; haemoptysis in 6 patients, pulmonary haemorrhage in 3 patients) with non-squamous NSCLC in the ramucirumab/DTX group and in 5 of 88 patients with non-squamous NSCLC (5.7%; haemoptysis in 5 patients) in the placebo/DTX group. Pulmonary haemorrhage in 1 patient with non-squamous NSCLC in the ramucirumab/DTX group was serious (Grade 3).

Table 13 shows the incidences of pulmonary haemorrhage-related adverse events classified by histology in the REVEL study.

Table 13. Pulmonary haemorrhage-related adverse events classified by histology of NSCLC in the REVEL study

Preferred term (MedDRA/J ver16.1)	Number of patients (%)							
	Squamous NSCLC				Non-squamous NSCLC			
	Ramucirumab/DTX (N = 157)		Placebo/DTX (N = 170)		Ramucirumab/DTX (N = 465)		Placebo/DTX (N = 441)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	15 (9.6)	3 (1.9)	21 (12.4)	4 (2.4)	34 (7.3)	5 (1.1)	25 (5.7)	4 (0.9)
Haemoptysis	11 (7.0)	1 (0.6)	16 (9.4)	2 (1.2)	25 (5.4)	3 (0.6)	16 (3.6)	2 (0.5)
Pulmonary haemorrhage	6 (3.8)	2 (1.3)	4 (2.4)	2 (1.2)	7 (1.5)	2 (0.4)	6 (1.4)	1 (0.2)
Laryngeal haemorrhage	0	0	1 (0.6)	0	3 (0.6)	0	3 (0.7)	0
Respiratory tract haemorrhage	0	0	0	0	0	0	1 (0.2)	1 (0.2)

In the ramucirumab/DTX group of the REVEL study, serious adverse events related to pulmonary haemorrhage were observed in 3 of 157 patients (1.9%) with squamous NSCLC and 6 of 465 patients (1.3%) with non-squamous NSCLC. Of these, 3 of 157 patients (1.9%) with squamous NSCLC and 3 of 465 patients (0.6%) with non-squamous NSCLC had a fatal outcome. In the placebo/DTX group of the REVEL study, serious adverse events related to pulmonary haemorrhage were observed in 6 of 170 patients (3.5%) with squamous NSCLC and 3 of 441 patients (0.7%) with non-squamous NSCLC. Of these, 3 of 170 patients (1.8%) with squamous NSCLC and in 3 of 441 patients (0.7%) with non-squamous NSCLC had a fatal outcome.

In the JVCG and REVEL studies, the incidences of pulmonary haemorrhage-related adverse events did not clearly differ between patient with squamous NSCLC and those with non-squamous NSCLC, and this suggests that histology is not a risk factor of ramucirumab-induced pulmonary haemorrhage. Patients with a risk factor for pulmonary haemorrhage (e.g., tumor invasion into major vessels or intratumoral cavitation in the chest, a history of haemoptysis) were excluded from both JVCG and REVEL studies regardless of the histology of NSCLC and therefore no safety findings in this patient group are available. This fact will be highlighted in the package insert for precautions.

PMDA's view:
The REVEL study showed no clear trend toward an increased incidence of pulmonary haemorrhage in the ramucirumab/DTX group as compared with the placebo/DTX group, regardless of the histology of NSCLC. However, fatal adverse events related to pulmonary haemorrhage occurred in patients treated with ramucirumab and their causal relationship to the study drug could not be ruled out. In addition, ramucirumab is an angiogenesis inhibitor. In light of these facts, patients on treatment with ramucirumab should be carefully monitored for pulmonary haemorrhage. Moreover, patients with a risk factor for pulmonary haemorrhage (e.g., tumor invasion into major vessels or intratumoral cavitation in the chest, a history of haemoptysis) were excluded from the clinical studies, precluding the adequate evaluation of the safety of ramucirumab in patients with such risk factors.

Based on the above, the occurrence of pulmonary haemorrhage-related adverse events in the clinical studies and the details of the exclusion criteria related to pulmonary haemorrhage risk factors should be appropriately included in the package insert for precautions. Further information on ramucirumab-associated pulmonary haemorrhage, including histology of NSCLC and the presence/absence of risk factors for pulmonary haemorrhage, should be collected via post-marketing surveillance. Any new findings should be communicated to healthcare professionals promptly when become available [see "7.R.6 Post-marketing investigations"].

7.R.4 Clinical positioning and indication

The proposed indication of ramucirumab was "unresectable advanced/recurrent non-small cell lung cancer." The "Precautions for Indications" section included the following descriptions:

- The efficacy and safety of ramucirumab in post-operative adjuvant chemotherapy have not been established.
- The efficacy and safety of ramucirumab in the first-line therapy have not been established.

- Eligibility of the patient for the treatment should be determined based on good understanding of the descriptions in the "Clinical Studies" section and of the efficacy and safety of ramucirumab.

PMDA's conclusion:
Based on the reviews below and in "7.R.2 Efficacy" and "7.R.3 Safety," the proposed descriptions of the "Indication" and "Precautions for Indications" sections for ramucirumab are acceptable.

7.R.4.1 Clinical positioning and target patients of ramucirumab

Japanese and foreign clinical practice guidelines and internationally recognized textbooks on clinical oncology describe ramucirumab for the treatment of unresectable advanced/recurrent NSCLC as follows.

Clinical practice guidelines

- NCCN Guideline (NSCLC) (v.4.2016):
  Based on the results of the REVEL study, ramucirumab/DTX is recommended for patients with unresectable advanced/recurrent NSCLC with a performance status (PS) of 0 to 2 and a history of platinum-based chemotherapy.

- The US National Cancer Institute Physician Data Query (NCI PDQ) (September 3, 2015):
  Based on the results of the REVEL study, ramucirumab is recommended for patients with unresectable advanced/recurrent NSCLC with a history of platinum-based chemotherapy.

Textbook

- DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology 10th edition (Lippincott Williams & Wilkins, 2015, USA):
  In the REVEL study in patients with NSCLC, ramucirumab was used as a second-line therapy and slightly prolonged survival.

The applicant's explanation on the indication of ramucirumab for the treatment of patients with unresectable advanced/recurrent NSCLC:
The REVEL study in patients with unresectable advanced/recurrent NSCLC with disease progression after first-line platinum-based chemotherapy demonstrated an add-on effect of ramucirumab to DTX, which contributed to prolonged OS [see "7.1.2.1 Foreign phase III study"]. Therefore ramucirumab can be a therapeutic option for the mentioned patient population.

The REVEL study excluded patients with a history of ≥2 chemotherapeutic regimens, and patients with a history of EGFR-TKI monotherapy were therefore not eligible for the study. Nevertheless, because of the following observations, ramucirumab is recommendable regardless of a history of EGFR-TKI monotherapy.

- The JVCG study enrolled 35 patients with a history of EGFR-TKI monotherapy (18 in the ramucirumab/DTX group, 17 in the placebo/DTX group). The median PFS assessed by the investigator (95% CI), the efficacy endpoint, was 5.65 (3.06, 9.92) months in the ramucirumab/DTX group and 4.37 (2.89, 9.86) months in the placebo/DTX group, with a hazard ratio (95% CI) of 0.68 (0.31, 1.48). The results suggest that ramucirumab is effective also in patients with a history of EGFR-TKI monotherapy.
- In Study JVCG, the safety profile of ramucirumab did not clearly differ between patients with and without a history of EGFR-TKI monotherapy (Table 14).

Table 14. Outline of safety (JVCG study, classified by history of EGFR-TKI monotherapy)

	Number of patients (%)			
	With history of EGFR-TKI monotherapy		Without history of EGFR-TKI monotherapy	
	Ramucirumab/DTX (N = 18)	Placebo/DTX (N = 17)	Ramucirumab/DTX (N = 76)	Placebo/DTX (N = 81)
All adverse events	18 (100)	17 (100)	76 (100)	81 (100)
Grade ≥3 adverse events	18 (100)	16 (94.1)	71 (93.4)	77 (95.1)
Adverse events resulting in death	0	0	1 (1.3)	1 (1.2)
Serious adverse events	6 (33.3)	4 (23.5)	22 (28.9)	27 (33.3)
Adverse events leading to treatment discontinuation	14 (77.8)	8 (47.1)	37 (48.7)	21 (25.9)
Adverse events leading to interruption	0	0	3 (3.9)	0
Adverse events leading to dose reduction	12 (66.7)	6 (35.3)	41 (53.9)	31 (38.3)

Accordingly, the indication was proposed as "unresectable advanced/recurrent non-small cell lung cancer." Patients with unresectable advanced/recurrent NSCLC with disease progression after first-line platinum-based chemotherapy were eligible for enrollment in the JVCG and REVEL studies. This will be included in the "Clinical Studies" section of the package insert and the following precautionary advice will be given in the "Precautions for Indications" section.

- The efficacy and safety of ramucirumab in the first-line therapy have not been established.
- Eligibility of the patient for the treatment should be determined based on good understanding of the descriptions in the "Clinical Studies" section and of the efficacy and safety of ramucirumab.

PMDA accepted the explanation of the applicant.

7.R.4.2 Efficacy and safety as a post-operative adjuvant chemotherapy

The applicant's explanation:
Currently, there are no clinical data available on the efficacy or safety of ramucirumab as a post-operative adjuvant chemotherapy, and the use of ramucirumab for such purpose is not recommended. This will be indicated in the "Precautions for Indications" section.

PMDA accepted the explanation of the applicant.

7.R.5 Dosage and administration

The proposed dosage and administration is "The usual adult dosage is 10 mg/kg (body weight) of ramucirumab (genetical recombination) administered as an intravenous infusion over approximately 60 minutes once every 3 weeks, in combination with docetaxel. The dose may be adjusted according to the conditions of the patient." The "Precautions for Dosage and Administration" section included the following.

- Advice to the effect that antineoplastic drugs to be used concomitantly with ramucirumab should be selected by physicians with a good understanding of the "Clinical Studies" section.
- Advice to the effect that the package inserts of the concomitant antineoplastic drugs should be read carefully before use.
- Premedication to alleviate infusion reaction
- Adjustment of infusion rate of ramucirumab to manage infusion reaction
- Guidelines for treatment interruption, dose reduction, discontinuation of ramucirumab, and dose reduction method in patients experiencing an adverse event
- Preparation method of the injection solution

Based on the following review as well as the review in "7.R.2 Efficacy" and "7.R.3 Safety," PMDA concluded that the proposed descriptions of "Dosage and Administration" and "Precautions for Dosage and Administration" sections were acceptable.

7.R.5.1 Dosage and administration

The applicant's justification for the dosage and administration of ramucirumab for unresectable advanced/recurrent NSCLC:

Based on the results of foreign phase I studies, etc., the dosing regimen of ramucirumab for the phase II and III studies was determined as ramucirumab 8 mg/kg every 2 weeks or ramucirumab 10 mg/kg every 3 weeks (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza Injection 500 mg"). In the JVCG and REVEL studies, ramucirumab was administered in combination with DTX, and ramucirumab 10 mg/kg was administered every 3 weeks in line with the dosing schedule of DTX. As a result, the clinical utility of ramucirumab in patients with unresectable advanced/recurrent NSCLC was demonstrated in the JVCG and REVEL studies. Therefore, the dosing regimen employed in these studies was proposed as the dosage and administration of ramucirumab.

In order to ensure appropriate selection of the dosage regimen of DTX to be used in combination with ramucirumab based on the results of clinical studies of ramucirumab, the "Precautions for Dosage and Administration" section will advise that antineoplastic drugs to be used in combination with ramucirumab should be selected by physicians with a good understanding of the "Clinical Studies" section and that the physicians should carefully read and understand the package inserts of the antineoplastic drugs before use.

PMDA accepted the explanation of the applicant.

7.R.5.2 Infusion rate and dose adjustment

The applicant's explanation on the guidelines for adjustment of infusion rate and dose of ramucirumab:

The JVCG and REVEL studies generally followed the criteria for infusion rate and for dose adjustment used in the RAINBOW study in patients with gastric cancer (approved indication), and thus demonstrated the efficacy and safety of ramucirumab. However, while ramucirumab was administered at 8 mg/kg in the RAINBOW study, a dose of 10 mg/kg was selected in both JVCG and REVEL studies. The method for dose reduction also differed. The dose in the JVCG and REVEL studies was first reduced from 10 mg/kg to 8 mg/kg and then to 6 mg/kg. In the RAINBOW study, however, the dose was first reduced from 8 mg/kg to 6 mg/kg, and then to 5 mg/kg.

Accordingly, the description of the "Precautions for Dosage and Administration" section will be the same as that for gastric cancer (approved indication), except for the dose reduction levels determined based on those for the JVCG and REVEL studies.

PMDA accepted the explanation of the applicant

7.R.5.3 Concomitant use with antineoplastic drugs other than DTX

The applicant's explanation on the concomitant use of ramucirumab with antineoplastic drugs other than DTX:

The efficacy and safety of ramucirumab in combination with antineoplastic drugs other than DTX have not been established in patients with unresectable advanced/recurrent NSCLC, and the combination is therefore not recommended. The "Dosage and Administration" section will advise the use of ramucirumab in combination with DTX.

PMDA accepted the applicant's explanation.

7.R.6 Post-marketing investigations

The applicant's explanation on the post-marketing surveillance plan:

In order to evaluate the safety, etc. of ramucirumab in the post-marketing setting, the applicant plans to conduct post-marketing surveillance in patients with unresectable advanced/recurrent NSCLC receiving ramucirumab.

In the surveillance, the important identified or potential risks defined at the initial approval of ramucirumab were selected as the key survey items, which consist of arterial thromboembolism, venous thromboembolism, infusion reaction, gastrointestinal perforation, haemorrhage, cardiac failure

congestive, disturbance of wound healing, fistula, posterior reversible encephalopathy syndrome, hypertension, proteinuria, and liver disorder/hepatic failure.

The planned sample size is 350 patients. It was determined based on the incidence of pulmonary haemorrhage in the JVCG study. Pulmonary haemorrhage is one of the key survey items and an adverse event requiring particular attention in patients with unresectable advanced/recurrent NSCLC, i.e., the patient population to be included in the surveillance. Given the incidences of adverse events reported in the JVCG and REVEL studies (for the key survey items), the sample size of 350 patients would be generally sufficient to obtain data on the key survey items other than haemorrhage (including pulmonary haemorrhage).

The observation period was set at 1 year because most of adverse events were observed within 1 year after the start of treatment with ramucirumab in the JVCG and REVEL studies.

PMDA's view:
Because of the following situations, post-marketing surveillance should be conducted to evaluate the safety, etc. of ramucirumab in patients with unresectable advanced/recurrent NSCLC in routine clinical practice in Japan. New safety and other findings should be communicated to healthcare professionals in an appropriate manner.

- Only limited information is available on the safety of ramucirumab in Japanese patients with NSCLC.
- Post-marketing surveillance in patients with unresectable advanced/recurrent gastric cancer (approved indication), is still underway and safety results of ramucirumab are unavailable.
- Ramucirumab caused serious FN, etc. more frequently in patients with NSCLC than in patients with gastric cancer. It is of a particular safety concern.

Because close attention must be paid to FN and pulmonary haemorrhage in patients on treatment with ramucirumab [see "7.R.3 Safety"], the surveillance should be designed to ensure that data on these adverse events are collected. Thus, FN should be added to the key survey items specified by the applicant, and the term "haemorrhage" should be modified to "haemorrhage (pulmonary haemorrhage in particular)." The target sample size and the observation period should be re-considered by taking account of the occurrences of the adverse events added to the key survey items.

7.3 Adverse events, etc. observed in clinical studies

This section summarizes major non-fatal adverse events identified from the clinical study data submitted for safety evaluation. Data on deaths reported are presented in "7.1 Evaluation data" and "7.2 Reference data." Since the data of Studies I4T-IE-JVBX, I4T-IE-JVCC, I4T-IE-JVBJ, and I4T-IE-JVBC and the RAINBOW study were submitted in support of the initial application (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza for Injection 500 mg"), they are omitted from this section.

7.3.1 Japanese phase II study (JVCG study)

Adverse events were observed in all patients. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 93 of 94 patients (98.9%) in the ramucirumab/DTX group and all patients in the placebo/DTX group. Table 15 shows adverse events with an incidence of ≥30% in either group.

Table 15. Adverse events with an incidence of ≥30% in either group

System organ class Preferred term (MedDRA/J ver.17.1)	Number of patients (%)			
	Ramucirumab/DTX (N = 94)		Placebo/DTX (N = 98)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	94 (100)	89 (94.7)	98 (100)	93 (94.9)
Blood and lymphatic system disorders				
Anaemia	37 (39.4)	3 (3.2)	40 (40.8)	3 (3.1)
FN	32 (34.0)	32 (34.0)	18 (18.4)	18 (18.4)
Neutropenia	17 (18.1)	16 (17.0)	30 (30.6)	27 (27.6)
Gastrointestinal disorders				
Stomatitis	51 (54.3)	6 (6.4)	31 (31.6)	1 (1.0)
Nausea	34 (36.2)	0	39 (39.8)	1 (1.0)
Diarrhoea	32 (34.0)	3 (3.2)	24 (24.5)	1 (1.0)
General disorders and administration site conditions				
Malaise	44 (46.8)	0	47 (48.0)	0
Oedema peripheral	34 (36.2)	1 (1.1)	27 (27.6)	0
Pyrexia	31 (33.0)	0	26 (26.5)	0
Fatigue	29 (30.9)	2 (2.1)	25 (25.5)	1 (1.0)
Investigations				
Neutrophil count decreased	73 (77.7)	69 (73.4)	69 (70.4)	63 (64.3)
White blood cell count decreased	73 (77.7)	60 (63.8)	68 (69.4)	54 (55.1)
Metabolism and nutrition disorders				
Decreased appetite	58 (61.7)	9 (9.6)	51 (52.0)	7 (7.1)
Respiratory, thoracic and mediastinal disorders				
Epistaxis	45 (47.9)	0	18 (18.4)	0
Skin and subcutaneous tissue disorders				
Alopecia	63 (67.0)	0	61 (62.2)	0

Serious adverse events were observed in 29.8% (28 of 94) of patients in the ramucirumab/DTX group and 31.6% (31 of 98) of patients in the placebo/DTX group. Serious adverse events reported by ≥2 patients in the ramucirumab/DTX group were FN in 8 patients (8.5%), decreased appetite in 4 patients (4.3%), pneumothorax in 3 patients (3.2%), metastases to meninges, pneumonitis, and general physical health deterioration in 2 patients (2.1%) each in the ramucirumab/DTX group. Serious adverse events reported by ≥2 patients in the placebo/DTX group were FN in 6 patients (6.1%), metastases to meninges in 4 patients (4.1%), pneumothorax and lung infection in 3 patients (3.1%) each, and interstitial lung disease in 2 patients (2.0%). A causal relationship to the study drug could not be ruled out for FN in 8 patients, pneumothorax in 3 patients, pneumonitis and decreased appetite in 2 patients each, and general physical health deterioration in 1 patient in the ramucirumab/DTX group; and FN in 6 patients, lung infection in 3 patients, and interstitial lung disease in 2 patients in the placebo/DTX group.

Adverse events led to discontinuation of the study drug in 51 of 94 patients (54.3%) in the ramucirumab/DTX group and 29 of 98 patients (29.6%) in the placebo/DTX group. Adverse events leading to discontinuation of the study drug reported by ≥3 patients in the ramucirumab/DTX group were neutrophil count decreased in 9 patients (9.6%), FN, oedema peripheral, and malaise in 4 patients (4.3%) each, pleural effusion, pneumonitis, and hypoalbuminaemia in 3 patients (3.2%) each. Adverse events leading to discontinuation of the study drug reported by ≥3 patients in the placebo/DTX group were FN in 4 patients (4.1%), oedema peripheral, pleural effusion, and pneumonitis in 3 patients (3.1%) each. A causal relationship to the study drug could not be ruled out for all events.

Adverse events led to interruption of the study drug in 3 of 94 patients (3.2%) in the ramucirumab/DTX group. All the 3 patients experienced proteinuria, and a causal relationship to the study drug could not be ruled out for the event.

Adverse events led to dose reduction of the study drug in 53 of 94 patients (56.4%) in the ramucirumab/DTX group and 37 of 98 patients (37.8%) in the placebo/DTX group. Adverse events leading to dose reduction reported by ≥2 patients in the ramucirumab/DTX group were neutrophil count decreased and FN in 24 patients (25.5%) each, proteinuria in 3 patients (3.2%), neutropenia, diarrhoea,

stomatitis, fatigue, and decreased appetite in 2 patients (2.1%) each. Adverse events leading to dose reduction reported by ≥2 patients in the placebo/DTX group were neutrophil count decreased in 17 patients (17.3%), FN in 15 patients (15.3%), neutropenia in 7 patients (7.1%), and leukopenia in 3 patients (3.1%). A causal relationship to the study drug could not be ruled out for neutrophil count decreased and FN in 24 patients each, proteinuria in 3 patients, neutropenia, diarrhoea, stomatitis, fatigue, and decreased appetite in 2 patients each in the ramucirumab/DTX group; and neutrophil count decreased in 16 patients, FN in 15 patients, neutropenia in 6 patients, and leukopenia in 2 patients in the placebo/DTX group.

7.3.2 Foreign phase II study (Study I4T-IE-JVBL)

Adverse events were observed in all patients in Group B (ramucirumab + PEM + platinum-based antineoplastic drug group) and in 68 of 69 patients (98.6%) in Group A (PEM + platinum-based antineoplastic drug group). Adverse events for which a causal relationship to the study drug could not be ruled out were observed in all patients in Group B and in 64 of 69 patients (92.8%) in Group A. Table 16 shows adverse events with an incidence of ≥20% in either group.

Table 16. Adverse events with an incidence of 20% in either group

System organ class Preferred term (MedDRA/J ver15.0)	Number of patients (%)			
	Group B (N = 67)		Group A (N = 69)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	67 (100)	54 (80.6)	68 (98.6)	53 (76.8)
Blood and lymphatic system disorders				
Thrombocytopenia	23 (34.3)	17 (25.4)	17 (24.6)	14 (20.3)
Neutropenia	24 (35.8)	14 (20.9)	16 (23.2)	13 (18.8)
Gastrointestinal disorders				
Diarrhoea	19 (28.4)	1 (1.5)	21 (30.4)	2 (2.9)
Nausea	35 (52.2)	7 (10.4)	39 (56.5)	5 (7.2)
Constipation	20 (29.9)	0	21 (30.4)	1 (1.4)
Vomiting	24 (35.8)	5 (7.5)	25 (36.2)	3 (4.3)
General disorders and administration site conditions				
Fatigue	44 (65.7)	8 (11.9)	43 (62.3)	12 (17.4)
Oedema peripheral	20 (29.9)	1 (1.5)	14 (20.3)	2 (2.9)
Metabolism and nutrition disorders				
Decreased appetite	20 (29.9)	2 (3.0)	18 (26.1)	1 (1.4)
Musculoskeletal and connective tissue disorders				
Back pain	16 (23.9)	7 (10.4)	9 (13.0)	1 (1.4)
Nervous system disorders				
Anaemia	31 (46.3)	8 (11.9)	38 (55.1)	12 (17.4)
Headache	19 (28.4)	1 (1.5)	8 (11.6)	0
Psychiatric disorders				
Insomnia	15 (22.4)	0	10 (14.5)	0
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	15 (22.4)	4 (6.0)	15 (21.7)	3 (4.3)
Epistaxis	17 (25.4)	0	5 (7.2)	0

Serious adverse events were observed in 42 of 67 patients (62.7%) in Group B and 37 of 69 patients (53.6%) in Group A. Serious adverse events reported by ≥3 patients in Group B were nausea, vomiting, and accidental overdose in 5 patients (7.5%) each, underdose, dehydration, and thrombocytopenia in 4 patients (6.0%) each, pleural effusion, overdose, and pulmonary embolism in 3 patients (4.5%) each. Serious adverse events reported by ≥3 patients in Group A were pneumonia in 6 patients (8.7%), nausea and vomiting in 4 patients (5.8%) each, and incorrect dose administered in 3 patients (4.3%). A causal relationship to the study drug could not be ruled out for nausea and thrombocytopenia in 4 patients each, vomiting, dehydration, and pulmonary embolism in 3 patients each in Group B; and nausea in 3 patients, vomiting and pneumonia in 2 patients each in Group A.

Adverse events led to the discontinuation of the study drug in 22 of 67 patients (32.8%) in Group B and 14 of 69 patients (20.3%) in Group A. Adverse events leading to the discontinuation of the study drug

reported by ≥2 patients in Group B were thrombocytopenia in 3 patients (4.5%), platelet count decreased and pulmonary embolism in 2 patients (3.0%) each. Adverse events leading to the discontinuation of the study drug reported by ≥2 patients in Group A were neutropenia and respiratory failure in 2 patients (2.9%) each. A causal relationship to the study drug could not be ruled out for thrombocytopenia in 3 patients, platelet count decreased and pulmonary embolism in 2 patients each in Group B; and neutropenia in 2 patients in Group A.

Adverse events led to dose reduction, interruption, or suspension in 39 of 67 patients (58.2%) in Group B and 30 of 69 patients (43.5%) in Group A. Adverse events leading to dose reduction, interruption, or suspension reported by ≥2 patients in Group B were thrombocytopenia in 14 patients (20.9%), anaemia in 12 patients (17.9%), neutropenia and fatigue in 8 patients (11.9%) each, hypertension in 4 patients (6.0%), nausea and dyspnoea in 3 patients (4.5%) each, platelet count decreased, asthenia, and thrombophlebitis in 2 patients (3.0%) each. Adverse events leading to dose reduction, interruption, or suspension reported by ≥2 patients in Group A were thrombocytopenia and anaemia in 10 patients (14.5%) each, neutropenia in 9 patients (13.0%), nausea, leukopenia, ALT increased, and haemoglobin decreased in 2 patients (2.9%) each. A causal relationship to the study drug could not be ruled out for thrombocytopenia in 14 patients, anaemia in 11 patients, neutropenia and fatigue in 8 patients each, hypertension in 3 patients, nausea, platelet count decreased, and asthenia in 2 patients each in Group B; and thrombocytopenia and anaemia in 10 patients each, neutropenia in 9 patients, leukopenia, ALT increased, and haemoglobin decreased in 2 patients each in Group A.

7.3.3 Foreign phase II study (Study I5B-IE-JGDE)

Adverse events were observed in 39 of 40 patients (97.5%) in the ramucirumab group and in all patients in the olaratumab (not approved in Japan) group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 36 of 40 patients (90.0%) in the ramucirumab group and 28 of 40 patients (70.0%) in the olaratumab group. Table 17 shows adverse events with an incidence of ≥20% in either group.

Table 17. Adverse events with an incidence of ≥20% in either group

System organ class Preferred term (MedDRA/J ver15.0)	Number of patients (%)			
	Ramucirumab (N = 40)		Olaratumab (N = 40)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	39 (97.5)	22 (55.0)	40 (100)	14 (35.0)
Gastrointestinal disorders				
Nausea	13 (32.5)	1 (2.5)	8 (20.0)	0
Diarrhoea	10 (25.0)	0	5 (12.5)	0
General disorders and administration site conditions				
Fatigue	19 (47.5)	4 (10.0)	19 (47.5)	2 (5.0)
Nervous system disorders				
Headache	13 (32.5)	3 (7.5)	16 (40.0)	1 (2.5)
Dizziness	8 (20.0)	0	5 (12.5)	0
Psychiatric disorders				
Insomnia	8 (20.0)	0	2 (5.0)	0
Vascular disorders				
Hypertension	10 (25.0)	5 (12.5)	2 (5.0)	0

Serious adverse events were observed in 14 of 40 patients (35.0%) in the ramucirumab group and 13 of 40 patients (32.5%) in the olaratumab group. Serious adverse events reported by ≥2 patients in the ramucirumab group were dehydration in 3 patients (7.5%) and deep vein thrombosis in 2 patients (5.0%). Serious adverse events reported by ≥2 patients in the olaratumab group were deep vein thrombosis and convulsion in 3 patients (7.5%) each, neoplasm progression, haemorrhage intracranial, pulmonary embolism, incorrect storage of drug, and medication error in 2 patients (5.0%) each. A causal relationship to the study drug could not be ruled out for dehydration in 3 patients and deep vein thrombosis in 1 patient in the ramucirumab group; and deep vein thrombosis and neoplasm progression in 2 patients each, convulsion, haemorrhage intracranial, and pulmonary embolism in 1 patient each in the olaratumab group.

Adverse events led to discontinuation of the study drug in 2 of 40 patients (5.0%) in the ramucirumab group and 3 of 40 patients (7.5%) in the olaratumab group. Platelet count decreased and shunt infection occurred in 1 patient (2.5%) each in the ramucirumab group, and thrombocytopenia in 2 patients (5.0%) and haemorrhage intracranial in 1 patient (2.5%) in the olaratumab group. A causal relationship to the study drug could not be ruled out for platelet count decreased in 1 patient in the ramucirumab group and thrombocytopenia in 2 patients and haemorrhage intracranial in 1 patient in the olaratumab group.

Adverse events led to dose reduction, interruption, or suspension of the study drug in 5 of 40 patients (12.5%) in the ramucirumab group and none in the olaratumab group. Platelet count decreased, thrombocytopenia, hypophosphataemia, depression, and hypertension occurred in 1 patient (2.5%) each in the ramucirumab group. A causal relationship to the study drug could not be ruled out for thrombocytopenia and hypophosphataemia in 1 patient each.

7.3.4 Foreign phase III study (REVEL study)

Adverse events were observed in 613 of 627 patients (97.8%) in the ramucirumab/DTX group and 594 of 618 patients (96.1%) in the placebo/DTX group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 579 of 627 patients (92.3%) in the ramucirumab/DTX group and 542 of 618 patients (87.7%) in the placebo/DTX group. Table 18 shows adverse events with an incidence of ≥20% in either group.

Table 18. Adverse events with an incidence of ≥20% in either group

System organ class Preferred term (MedDRA/J ver16.)	Number of patients (%)			
	Ramucirumab/DTX (N = 627)		Placebo/DTX (N = 618)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	613 (97.8)	495 (78.9)	594 (96.1)	444 (71.8)
Blood and lymphatic system disorders				
Neutropenia	244 (38.9)	219 (34.9)	205 (33.2)	173 (28.0)
Anaemia	131 (20.9)	18 (2.9)	171 (27.7)	34 (5.5)
Gastrointestinal disorders				
Diarrhoea	199 (31.7)	29 (4.6)	171 (27.7)	19 (3.1)
Nausea	169 (27.0)	7 (1.1)	170 (27.5)	9 (1.5)
Stomatitis	146 (23.3)	27 (4.3)	80 (12.9)	10 (1.6)
General disorders and administration site conditions				
Fatigue	289 (46.1)	71 (11.3)	258 (41.7)	50 (8.1)
Metabolism and nutrition disorders				
Decreased appetite	182 (29.0)	14 (2.2)	154 (24.9)	8 (1.3)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	138 (22.0)	24 (3.8)	149 (24.1)	51 (8.3)
Cough	133 (21.2)	3 (0.5)	128 (20.7)	5 (0.8)
Skin and subcutaneous tissue disorders				
Alopecia	162 (25.8)	0	156 (25.2)	0

Serious adverse events were observed in 269 of 627 patients (42.9%) in the ramucirumab/DTX group and 262 of 618 patients (42.4%) in the placebo/DTX group. Serious adverse events with an incidence of ≥2% in the ramucirumab/DTX group were FN in 86 patients (13.7%), pneumonia in 36 patients (5.7%), neutropenia in 30 patients (4.8%), dehydration and stomatitis in 14 patients (2.2%) each, and diarrhoea in 13 patients (2.1%). Serious adverse events with an incidence of ≥2% in the placebo/DTX group were FN in 51 patients (8.3%), pneumonia in 33 patients (5.3%), neutropenia in 27 patients (4.4%), dyspnoea and pleural effusion in 20 patients (3.2%) each, and anaemia in 14 patients (2.3%). A causal relationship to the study drug could not be ruled out for FN in 86 patients, neutropenia in 29 patients, pneumonia in 17 patients, stomatitis in 14 patients, dehydration and diarrhoea in 12 patients each in the ramucirumab/DTX group; and FN in 50 patients, neutropenia in 27 patients, anaemia in 11, pneumonia in 7 patients, pleural effusion in 4 patients, and dyspnoea in 2 patients in the placebo/DTX group.

Adverse events led to discontinuation of the study drug in 132 of 627 patients (21.1%) in the ramucirumab/DTX group and 83 of 618 patients (13.4%) in the placebo/DTX group. Adverse events

leading to discontinuation of the study drug reported by ≥5 patients in the ramucirumab/DTX group were fatigue in 14 patients (2.2%), neutropenia, peripheral sensory neuropathy, and infusion related reaction in 7 patients (1.1%) each, thrombocytopenia in 6 patients (1.0%), platelet count decreased, asthenia, and peripheral motor neuropathy in 5 patients (0.8%) each. Adverse events leading to discontinuation of the study drug reported by ≥5 patients in the placebo/DTX group were neutropenia in 6 patients (1.0%) and drug hypersensitivity in 5 patients (0.8%). A causal relationship to the study drug could not be ruled out for fatigue in 14 patients, neutropenia and infusion related reaction in 7 patients each, peripheral sensory neuropathy in 6 patients, thrombocytopenia and peripheral motor neuropathy in 5 patients each, and thrombocytopenia and asthenia in 4 patients each in the ramucirumab/DTX group; and neutropenia in 6 patients and drug hypersensitivity in 5 patients in the placebo/DTX group.

Adverse events led to treatment interruption in 8 of 627 patients (1.3%) in the ramucirumab/DTX group and 7 of 618 patients (1.1%) in the placebo/DTX group. Adverse events leading to treatment interruption in the ramucirumab/DTX group were tachycardia, hypersensitivity, device related infection, infusion related reaction, proteinuria, skin hyperpigmentation, endodontic procedure, flushing, and hypertension in 1 patient (0.2%) each. Adverse events leading to treatment interruption in the placebo/DTX group were haemoptysis in 2 patients (0.3%), neutropenia, fatigue, neuropathy peripheral, peripheral sensory neuropathy, and rash in 1 patient (0.2%) each. A causal relationship to the study drug could not be ruled out for tachycardia, hypersensitivity, device related infection, infusion related reaction, proteinuria, skin hyperpigmentation, flushing, and hypertension in 1 patient each in the ramucirumab/DTX group; and fatigue, neuropathy peripheral, peripheral sensory neuropathy, and rash in 1 patient each in the placebo/DTX group.

Adverse events led to dose reduction of the study drug in 180 of 627 patients (28.7%) in the ramucirumab/DTX group and 130 of 618 patients (21.0%) in the placebo/DTX group. Adverse events leading to dose reduction of the study drug reported by ≥3 patients in the ramucirumab/DTX group were neutropenia in 54 patients (8.6%), FN in 41 patients (6.5%), fatigue in 23 patients (3.7%), neutrophil count decreased and weight decreased in 12 patients (1.9%) each, mucosal inflammation in 11 patients (1.8%), asthenia in 6 patients (1.0%), stomatitis in 5 patients (0.8%), diarrhoea in 4 patients (0.6%), leukopenia, decreased appetite, and thrombocytopenia in 3 patients (0.5%) each. Adverse events leading to dose reduction of the study drug reported by ≥3 patients in the placebo/DTX group were neutropenia in 37 patients (6.0%), FN in 28 patients (4.5%), fatigue in 13 patients (2.1%), neutrophil count decreased in 11 patients (1.8%), weight decreased in 6 patients (1.0%), stomatitis, diarrhoea, and drug hypersensitivity in 4 patients (0.6%) each, and dehydration in 3 patients (0.5%). A causal relationship to the study drug could not be ruled out for neutropenia in 54 patients, FN in 41 patients, fatigue in 21 patients, neutrophil count decreased in 12 patients, mucosal inflammation in 10 patients, weight decreased in 9 patients, asthenia in 6 patients, stomatitis in 5 patients, diarrhoea in 4 patients, decreased appetite and thrombocytopenia in 3 patients each, and leukopenia in 2 patients in the ramucirumab/DTX group; and neutropenia in 36 patients, FN in 28 patients, fatigue in 13 patients, neutrophil count decreased in 9 patients, diarrhoea and drug hypersensitivity in 4 patients each, stomatitis and dehydration in 3 patients each, and weight decreased in 1 patient in the placebo/DTX group.

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 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. The inspection and assessment revealed no noteworthy issues. PMDA thus 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 on-site GCP inspection

The new drug application data (CTD 5.3.5.1.2) were subjected to an on-site 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. PMDA concluded that the clinical studies as a whole were conducted in compliance with GCP and that there were no obstacles to conducting its review based on the application documents submitted. The following finding was noted at a study site (medical institution). Although the finding did not significantly affect the overall evaluation of the study, it was notified to the head of the pertinent study sites to seek improvement.

Matter to be improved

Medical institution

- Protocol deviation (incompliance with the rules for the administration of study drug)

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

PMDA concluded that the data submitted demonstrate the efficacy of ramucirumab (Cyramza) in the treatment of patients with unresectable advanced/recurrent NSCLC and acceptable safety in view of the benefits indicated. Ramucirumab has a clinical significance as a therapeutic option for unresectable advanced/recurrent NSCLC. Also, the post-marketing investigations should be further discussed.

This application may be approved if ramucirumab is not considered to have particular problems based on comments from the Expert Discussion.

Review Report (2)

May 16, 2016

Product Submitted for Approval

Brand Name	Cyramza Injection 100 mg Cyramza Injection 500 mg
Non-proprietary Name	Ramucirumab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of Application	July 23, 2015

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

PMDA's conclusions:

As reviewed in "7.R.2 Efficacy" of the Review Report (1), overall survival (OS) was assessed as the primary endpoint of the foreign phase III study (REVEL study) in patients with advanced/recurrent non-small cell lung cancer (NSCLC) with disease progression after first-line platinum-based chemotherapy. Ramucirumab (Genetical Recombination) (hereinafter referred to as "ramucirumab") plus docetaxel hydrate (DTX) achieved a significant improvement in OS as compared with placebo plus DTX as the control. Thus, the study demonstrated the efficacy of ramucirumab in this patient population. Based on the results of the Japanese phase II study (JVCG study) in Japanese patients with similar disease conditions to patients enrolled in the REVEL study, ramucirumab is expected to be effective in Japanese patients as well.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.2 Safety

PMDA's conclusions:

As reviewed in "7.R.3 Safety" of the Review Report (1), febrile neutropenia and pulmonary haemorrhage are adverse events requiring special attention during treatment with ramucirumab, as with those identified at the review of the initial application (i.e., hypertension, proteinuria, haemorrhage, infusion-related reaction, thromboembolism, gastrointestinal perforation, cardiac failure congestive, neutropenia/leukopenia, posterior reversible encephalopathy syndrome, fistula, disturbance of wound healing, and liver disorder).

Ramucirumab is well tolerated when patients are followed by physicians with sufficient knowledge of and experience with cancer chemotherapy, through monitoring and control of adverse events as well as appropriate measures including interruption, dose reduction, or discontinuation of ramucirumab.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indication

PMDA's conclusions:

As reviewed in "7.R.4 Clinical positioning and indication" of the Review Report (1), ramucirumab is a therapeutic option for the patient population assessed in the REVEL study. Ramucirumab should be indicated for "unresectable advanced/recurrent non-small cell lung cancer," as proposed by the applicant.

The patient population enrolled in the REVEL study should be specifically described in the "Clinical Studies" section of the package insert. Further, the following precautionary advice should be given in the "Precautions for Indications" section.

- The efficacy and safety of ramucirumab in post-operative adjuvant chemotherapy have not been established.
- The efficacy and safety of ramucirumab in the first-line therapy have not been established.
- Eligibility of the patient for the treatment should be determined based on good understanding of the "Clinical Studies" section and of the efficacy and safety of ramucirumab.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

Accordingly, PMDA advised the applicant to describe the "Indication" and "Precautions for Indication" sections as above, and the applicant agreed.

1.4 Dosage and administration

PMDA's conclusions:
As reviewed in "7.R.5 Dosage and administration" of the Review Report (1), the following proposed descriptions of the "Dosage and Administration" and "Precautions for Dosage and Administration" sections are acceptable.

[Dosage and Administration]
The usual adult dosage is 10 mg/kg (body weight) of Ramucirumab (Genetical Recombination) administered as an intravenous infusion over approximately 60 minutes every 3 weeks, in combination with docetaxel. The dose may be adjusted according to the condition of the patient.

[Precautions for Dosage and Administration]

- Advice to the effect that antineoplastic drugs to be used concomitantly with ramucirumab should be selected by physicians with a good understanding the descriptions of the "Clinical Studies" section.
- Advice to the effect that the package inserts of the concomitant antineoplastic drugs should be read carefully before use.
- Premedication to alleviate infusion reaction
- Adjustment of infusion rate of ramucirumab to manage infusion reaction
- Guidelines for interruption, dose reduction, or discontinuation of ramucirumab, and dose reduction method in patients experiencing an adverse event
- Preparation method of the injection solution

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

Accordingly, PMDA advised the applicant to describe the "Dosage and Administration" and "Precautions for Dosage and Administration" sections as above, and the applicant agreed.

1.5 Risk management plan (draft)

In order to investigate the safety of ramucirumab in post-marketing clinical use, the applicant plans to conduct post-marketing surveillance targeting patients with unresectable advanced/recurrent NSCLC who are treated with ramucirumab.

PMDA's conclusions:
As reviewed in "7.R.6 Post-marketing investigations" of the Review Report (1), post-marketing surveillance should be conducted to evaluate the safety, etc. of ramucirumab in clinical use. Any safety findings should be appropriately communicated to healthcare professionals.

The following should be noted in planning of the surveillance:

- Febrile neutropenia should be added to the key survey items determined by the applicant. Also, the description of "haemorrhage" should be modified to "haemorrhage (pulmonary haemorrhage in particular)."
- The target sample size and the observation period should be reconsidered taking account of the incidences, etc. of the adverse event identified additionally as a key survey item.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion. The following comment was raised by expert advisors:
- Patients who have experienced pulmonary haemorrhage should be investigated for their characteristics such as presence/absence of risk factors.

Accordingly, PMDA advised the applicant to re-consider their surveillance plan.

The applicant's response:
- Febrile neutropenia will be added to the key survey items, and haemorrhage will be more specifically described as "haemorrhage (pulmonary haemorrhage in particular)."
- The planned sample size will be 350 patients based on the incidence of pulmonary haemorrhage in the JVCG study. Pulmonary haemorrhage is the adverse event requiring special attention in patients with unresectable advanced/recurrent NSCLC (i.e., the patient population to be included in the surveillance). In the JVCG study, febrile neutropenia, the additional key survey item, occurred more frequently than pulmonary haemorrhage. The planned sample size of 350 patients will be sufficient to investigate febrile neutropenia as well.
- The observation period will be set at 1 year, taking account of the time to onset of the adverse events included in the key survey items.
- Parameters that may be risk factors for pulmonary haemorrhage associated with the use of angiogenesis inhibitors like ramucirumab will be included in the survey items to investigate the characteristics of patients who have experienced pulmonary haemorrhage.

PMDA accepted the response of the applicant.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for ramucirumab should include safety and efficacy specifications presented in Table 19, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 20.

Table 19. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hypertension • Proteinuria • Haemorrhage • Infusion reaction • Arterial thromboembolism • Venous thromboembolism • Gastrointestinal perforation • Congestive cardiac failure • Neutropenia/febrile neutropenia/ leukopenia • Posterior reversible encephalopathy syndrome • Fistula • Disturbance of wound healing	• Liver disorder/hepatic failure	• Not applicable
Efficacy specification (matters related to the present application for partial change)		
• Efficacy in patients with unresectable advanced/recurrent NSCLC in routine clinical practice		

Table 20. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Specified use-results survey in patients with unresectable advanced/recurrent NSCLC • Specified use-results survey in patients with unresectable advanced/recurrent gastric cancer	• Preparation and supply of materials for healthcare professionals

Underlines denote planned activities for the additional indication in the present application.

Table 21. Outline of use-results survey (draft)

Objective	To evaluate safety, etc. of ramucirumab in routine clinical practice
Survey method	Continuous registration
Population	Patients with unresectable advanced/recurrent NSCLC
Observation period	1 year from the start of treatment
Planned sample size	350
Main survey items	Key survey items: Hypertension, proteinuria, haemorrhage (pulmonary haemorrhage in particular), infusion reaction, arterial thromboembolism, venous thromboembolism, gastrointestinal perforation, congestive cardiac failure, posterior reversible encephalopathy syndrome, fistula, disturbance of wound healing, liver disorder/hepatic failure, and febrile neutropenia Other main survey items: Patient characteristics (body weight, medical history, complication, histology, clinical stage, site of metastasis/relapse, etc.), past treatment, use of ramucirumab, concomitant drugs and therapies, survival status, adverse events, etc.

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 modified as below, with the following condition for approval. However, (i) the package insert should include appropriate precautionary advice, and information on the proper use of the product should be adequately communicated to healthcare professionals in the post-marketing setting, and (ii) the product should be properly used by physicians with sufficient knowledge of and experience with cancer chemotherapy at medical institutions well-prepared for emergencies. The re-examination period for the present application is the remainder of the 8-year re-examination period for the initial approval of the product (until March 25, 2023).

[Indications] (Underline denotes addition.)
Unresectable advanced/recurrent gastric cancer
Unresectable advanced/recurrent non-small cell lung cancer

[Dosage and administration] (Underline denotes addition.)
1. Unresectable advanced/recurrent gastric cancer

The usual adult dosage is 8 mg/kg (body weight) of Ramucirumab (Genetical Recombination) administered as an intravenous infusion over approximately 60 minutes every 2 weeks. The dose may be adjusted according to the condition of the patient.

2. Unresectable advanced/recurrent non-small cell lung cancer

The usual adult dosage is 10 mg/kg (body weight) of ramucirumab (genetical recombination) administered as an intravenous infusion over approximately 60 minutes every 3 weeks, in combination with docetaxel. The dose may be adjusted according to the condition of the patient.

[Condition for approval]
The applicant is required to design and appropriately implement a risk management plan.

[Warnings] (No change)
1. Ramucirumab should be administered only to patients considered to be eligible for ramucirumab therapy by a physician with sufficient knowledge and experience with cancer chemotherapy and at a medical institution that is able to properly respond to emergencies. The benefits and risks of the therapy should be thoroughly explained to the patient or their family member, and consent should be obtained prior to treatment.

2. Serious arterial thromboembolism such as myocardial infarction and cerebrovascular disorder has been reported with some fatal cases. Patients should be carefully monitored and, in case of any abnormality, ramucirumab should be discontinued and appropriate measures should be taken. If severe arterial thromboembolism occurs, treatment with ramucirumab should not be resumed.

3. Severe gastrointestinal haemorrhage has been reported with some fatal cases. Patients should be carefully monitored and, in case of any abnormality, ramucirumab should be discontinued and appropriate measures should be taken. If severe haemorrhage occurs, treatment with ramucirumab should not be resumed.

4. Gastrointestinal perforation has been reported with some fatal cases. Patients should be carefully monitored and, if any abnormalities are observed, ramucirumab should be discontinued and appropriate measures should be taken. If gastrointestinal perforation occurs, treatment with ramucirumab should not be resumed.

[Contraindications] (No change)
1. Patients with a history of serious hypersensitivity to any ingredient in ramucirumab

2. Pregnant women or women who may be pregnant

[Precautions for indications] (Underline denotes addition.)
1. The efficacy and safety of ramucirumab in post-operative adjuvant chemotherapy have not been established.

2. The efficacy and safety of ramucirumab in first-line chemotherapy have not been established.

3. For unresectable advanced/recurrent gastric cancer, eligibility of the patient for the treatment should be determined based on good understanding of the descriptions in the "Clinical Studies" section (particularly the information about primary lesions) and of the efficacy and safety of ramucirumab.

4. For unresectable advanced/recurrent non-small cell lung cancer, eligibility of the patient for the treatment should be determined based on good understanding of the descriptions in the "Clinical Studies" section and of the efficacy and safety of ramucirumab.

[Precautions for dosage and administration] (Underline denotes added text, and strike-through denotes deleted text.)
1. For unresectable advanced/recurrent gastric cancer, the efficacy and safety of ramucirumab in combination with antineoplastic drugs other than paclitaxel have not been established.

2. For unresectable advanced/recurrent non-small cell lung cancer, antineoplastic drugs to be used concomitantly with ramucirumab should be selected by physicians with a good understanding of the descriptions of the "Clinical Studies" section.

3. The package inserts of the concomitant antineoplastic drugs should be read carefully before use.

~~2~~4. For the purpose of mitigating infusion reactions associated with ramucirumab, premedication with an antihistaminic drug (e.g., diphenhydramine) should be considered. If a Grade[Note 1)] 1 or 2 infusion reaction occurs, the patient should be treated with an antihistaminic drug before all subsequent infusion of ramucirumab. If a Grade[Note 1)] 1 or 2 infusion reaction recurs even with the premedication, an antipyretic analgesic (e.g., acetaminophen) and a corticosteroid (e.g., dexamethasone) should be administered in addition to the antihistaminic drug before ramucirumab.

~~3~~5. In case of a Grade[Note 1)] 3 or 4 infusion reaction, the administration of ramucirumab should be discontinued immediately and should not be resumed. In case of a Grade[Note 1)] 1 or 2 infusion reaction, the infusion rate should be reduced by 50%, and the reduced infusion rate should be maintained with all subsequent doses.

4~~6~~. In case of hypertension or proteinuria, the administration of ramucirumab should be interrupted or discontinued, or the dose of ramucirumab should be reduced according to the criteria below.

Adverse drug reaction		Measure to be taken
Hypertension	Symptomatic Grade[Note 1)] 2, or Grade [Note 1)] ≥3	Give anti-hypertensive treatment. Interrupt treatment with ramucirumab until blood pressure is appropriately controlled. If the anti-hypertensive treatment fails to control blood pressure, discontinue ramucirumab.
Proteinuria	24-hour urine protein ≥2 g[Note 2)]	First episode: Interrupt the treatment until 24-hour urine protein decreases to <2 g [Note 2)], then resume the treatment at the following reduced dose: • 6 mg/kg if the initial dose is 8 mg/kg. • 8 mg/kg if the initial dose is 10 mg/kg.
		Second and subsequent episodes: Interrupt the treatment until 24-hour urine protein decreases to <2 g [Note 2)], then resume the treatment at the following reduced dose: • 5 mg/kg if the initial dose is 8 mg/kg. • 6 mg/kg if the initial dose is 10 mg/kg.
	24-hour urine protein ≥3 g[Note 2)] or an episode of nephrotic syndrome	Discontinue treatment.

[Note 1)]: Common Terminology Criteria for Adverse Events (ver.4.0)
[Note 2)]: An all-urine test with 24-hour urine collection is desirable. If unfeasible, protein/creatinine ratio in urine should be determined.

5~~7~~. Preparation method for the injection solution
Prior to administration, the required volume of ramucirumab is calculated and is withdrawn with a syringe. It is then mixed with normal saline (JP) so that the total volume of 250 mL of solution is made in a container for intravenous infusion. The infusion solution should be thoroughly mixed.