Report on the Deliberation Results

March 8, 2018

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Lenvima Capsules 4 mg
Non-proprietary Name	Lenvatinib Mesilate (JAN*)
Applicant	Eisai Co., Ltd.
Date of Application	June 23, 2017

Results of Deliberation

In its meeting held on March 2, 2018, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 5 years and 10 months.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

February 14, 2018
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Lenvima Capsules 4 mg
Non-proprietary name	Lenvatinib Mesilate
Applicant	Eisai Co., Ltd.
Date of Application	June 23, 2017
Dosage Form/Strength	Each capsule contains 4.90 mg of Lenvatinib Mesilate (4 mg of lenvatinib).
Application Classification	Prescription drug (4) Drug with a new indication, (6) Drug with a new dosage
Reviewing Office	Office of New Drug V

Results of Review
On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with unresectable hepatocellular carcinoma, and that the product has acceptable safety in view of its benefits (see 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 condition. The occurrence of hepatic encephalopathy needs to be further investigated via post-marketing surveillance.

Indications
Unresectable thyroid cancer, unresectable hepatocellular carcinoma

(Underline denotes addition.)

Dosage and Administration
Unresectable thyroid cancer
The usual adult dosage is 24 mg of lenvatinib administered orally once daily. The dose may be reduced according to the patient's condition.

Unresectable hepatocellular carcinoma

The usual adult dosage is determined according to the body weight; 12 mg for patients weighing ≥60 kg or 8 mg for patients weighing <60 kg, administered orally once daily. The dose may be reduced according to the patient's condition.

(Underline denotes addition.)

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

January 12, 2018

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	Lenvima Capsules 4 mg
Non-proprietary Name	Lenvatinib Mesilate
Applicant	Eisai Co., Ltd.
Date of Application	June 23, 2017
Dosage Form/Strength	Each capsule contains 4.90 mg of Lenvatinib Mesilate (4 mg of lenvatinib).
Proposed Indications	Unresectable thyroid cancer, unresectable hepatocellular carcinoma

(Underline denotes addition.)

Proposed Dosage and Administration

Unresectable thyroid cancer

The usual adult dosage is 24 mg of lenvatinib administered orally once daily. The dose may be reduced according to the patient's condition.

Unresectable hepatocellular carcinoma

The usual adult dosage is determined according to the body weight. The following dosage of lenvatinib is administered orally once daily; 12 mg for patients weighing ≥60 kg or 8 mg for patients weighing <60 kg. The dose may be reduced according to the patient's condition.

(Underline denotes addition.)

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Overview of the product submitted for approval

Lenvatinib Mesilate (hereinafter referred to as lenvatinib), discovered by the applicant, is a low molecular weight chemical compound that inhibits kinases such as vascular endothelial growth factor receptor (VEGFR) 1, VEGFR2, and VEGFR3, rearranged during transfection (RET) gene product, fibroblast growth factor receptor (FGFR) 1, FGFR2, FGFR3, and 4, platelet-derived growth factor receptor (PDGFR) α, and stem cell factor receptor (KIT). Lenvatinib is considered to suppress tumor proliferation by inhibiting the concerned kinase-mediated signal transduction.

In Japan, lenvatinib was approved for the indication of "unresectable thyroid cancer" in March 2015.

1.2 Development history, etc.

The applicant initiated a global phase I/II study (Study E7080-J081-202 [Study 202]) in patients with unresectable hepatocellular carcinoma in July 2009 to proceed with clinical development of lenvatinib for treatment of hepatocellular carcinoma. In addition, the applicant initiated a global phase III study (Study E7080-G000-304 [Study 304]) in patients with unresectable hepatocellular carcinoma in March 2013.

In Japan, the partial change application for lenvatinib to add an indication of unresectable hepatocellular carcinoma has been filed mainly based on results from Study 304. In the US and EU, an application for lenvatinib was filed in July 2017 mainly based on results from Study 304 as well after submission of the partial change application in Japan. As of November in 2017, lenvatinib has not been approved for the indication of hepatocellular carcinoma in any country or region.

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

Since this application is intended for addition of new indication and dosages, no data relating to quality were submitted.

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

3.1 Primary pharmacodynamics

3.1.1 Binding to FGFR (CTD 4.2.1.1.1)

Binding of lenvatinib to recombinant human FGFR1 protein was investigated by X-ray crystallography. The results suggested that lenvatinib bound to adenosine triphosphate (ATP) binding site and allosteric region of the kinase domain of FGFR1.

3.1.2 Inhibitory effect against angioid tube formation (CTD 4.2.1.1.3)

An inhibitory effect of lenvatinib against angioid tube formation induced by fibroblast growth factor (FGF) was investigated using human umbilical vein endothelial cells (HUVEC). In this investigation, the inhibitory rate[1)] against the concerned tube formation was used as an indicator. The IC_{50} value of lenvatinib (mean, 95% confidence interval [CI], n = 3) was 7.3 (2.1, 26) nmol/L.

1) Inhibitory rate (%) = (mean length of formed angioid tube in the control medium [containing dimethyl sulfoxide (DMSO) at 0.1%] – mean length of formed angioid tube in the medium containing lenvatinib) / mean length of formed angioid tube in the control medium) × 100

3.1.3 Inhibitory effect against FGF-mediated signal transduction (CTD 4.2.1.1.5, 4.2.1.1.6, 4.2.1.1.7, 4.2.1.1.8)

An inhibitory effect of lenvatinib against phosphorylation of extracellular signal-regulated kinase (ERK) 1/2, ribosomal protein S6 kinase (S6K), and ribosomal protein S6 (S6), downstream signaling molecules of FGFR, was investigated by Western blotting. The results showed that lenvatinib inhibited phosphorylation of ERK1/2 (T202/Y204[2)]), S6K (T389[3)]), S6K (T421/S424[4)]), and S6 (S235/S236[5)]).

An inhibitory effect of lenvatinib against phosphorylation of fibroblast growth factor receptor substrate 2 (FRS2), downstream signaling molecule of FGFR, was investigated using human hepatocellular carcinoma-derived Hep 3B2.1-7, HuH-7, and SNU-449 cell lines by Western blotting. The results showed that lenvatinib inhibited phosphorylation of FRS2 (Y436[6)]) in these cell lines.

3.1.4 Antiproliferative effect against malignant tumor-derived cell lines

3.1.4.1 *In vitro* (CTD 4.2.1.1.9)

An antiproliferative effect of lenvatinib was investigated using Hep 3B2.1-7, HuH-7, and human hepatocellular carcinoma-derived PLC/PRF/5 cell lines. In this investigation, viable cell count measured with a reducing dye was used as an indicator. The IC_{50} values of lenvatinib (mean, 95% CI, n = 3) against the above cell lines were 230 (160, 320), 420 (320, 550), and >10,000 nmol/L, respectively.

3.1.4.2 *In vivo* (CTD 4.2.1.1.12, 4.2.1.1.14, 4.2.1.1.16, 4.2.1.1.17, 4.2.1.1.18)

A tumor growth inhibitory effect of lenvatinib was investigated using nude mice (n = 6/group) subcutaneously transplanted with PLC/PRF/5 cell line. Administration was started on 10 days after the transplantation (Day 1). Lenvatinib at 1, 3, 10, 30, or 100 mg/kg was administered orally quaque die (QD) for 14 days to the nude mice, and on Day 15, the tumor volume was calculated. A statistically significant tumor growth inhibitory effect was observed in the lenvatinib 3, 10, 30, and 100 mg/kg groups in comparison with the vehicle (distilled water) group ($P < 0.05$, Dunnett's multiple comparison test).

A tumor growth inhibitory effect of lenvatinib was investigated using nude mice (n = 8/group) subcutaneously transplanted with Hep 3B2.1-7 cell line. Administration was started on 12 days after the transplantation (Day 1). Lenvatinib at 3, 10, or 30 mg/kg was administered orally QD for 7 days to the nude mice, and on Day 8, the tumor volume was calculated. A statistically significant tumor growth inhibitory effect was observed in all the lenvatinib groups in comparison with the vehicle (3 mmol/L hydrochloric acid solution) group ($P < 0.0001$, Dunnett's multiple comparison test).

A tumor growth inhibitory effect of lenvatinib was investigated using nude mice (n = 8/group) subcutaneously transplanted with human hepatocellular carcinoma-derived LIXC-012 cell line. Administration was started on 11 days after the transplantation (Day 1). Lenvatinib at 3, 10, or 30 mg/kg was administered orally QD for 14 days to the nude mice, and on Day 11, the tumor volume was

2) Threonine residue at position 202 and tyrosine residue at position 204 of ERK1/2
3) Threonine residue at position 389 of S6K
4) Threonine residue at position 421 and serine residue at position 424 of S6K
5) Serine residues at positions 235 and 236 of S6
6) Tyrosine residue at position 436 of FRS2

calculated. A statistically significant tumor growth inhibitory effect was observed in all the lenvatinib groups in comparison with the vehicle (3 mmol/L hydrochloric acid solution) group ($P < 0.001$, Bonferroni's multiple comparison test).

Tumor growth inhibitory effects of lenvatinib and sorafenib tosilate (sorafenib) were investigated using nude mice (n = 15/group) subcutaneously transplanted with tumor tissue fragments (LI0050) derived from a patient with hepatocellular carcinoma. Administration was started on 19 days after the transplantation (Day 1). Lenvatinib at 10 or 30 mg/kg or sorafenib at 30 mg/kg was administered orally QD for 28 days to the nude mice, and on Day 29, the tumor volume was calculated. A statistically significant tumor growth inhibitory effect was observed in all the lenvatinib groups in comparison with the vehicle (3 mmol/L hydrochloric acid solution) group ($P < 0.001$, Dunnett's multiple comparison test) (Figure 1, left).

Tumor growth inhibitory effects of lenvatinib and sorafenib were investigated using nude mice (n = 15/group) subcutaneously transplanted with tumor tissue fragments (LI0334) derived from a patient with hepatocellular carcinoma. Administration was started on 46 days after the transplantation (Day 1). Lenvatinib at 10 or 30 mg/kg or sorafenib at 30 mg/kg was administered orally QD for 28 days to the nude mice, and on Day 29, the tumor volume was calculated. A statistically significant tumor growth inhibitory effect was observed in all the lenvatinib groups in comparison with the vehicle (3 mmol/L hydrochloric acid solution) group ($P < 0.001$, Dunnett's multiple comparison test) (Figure 1, right).

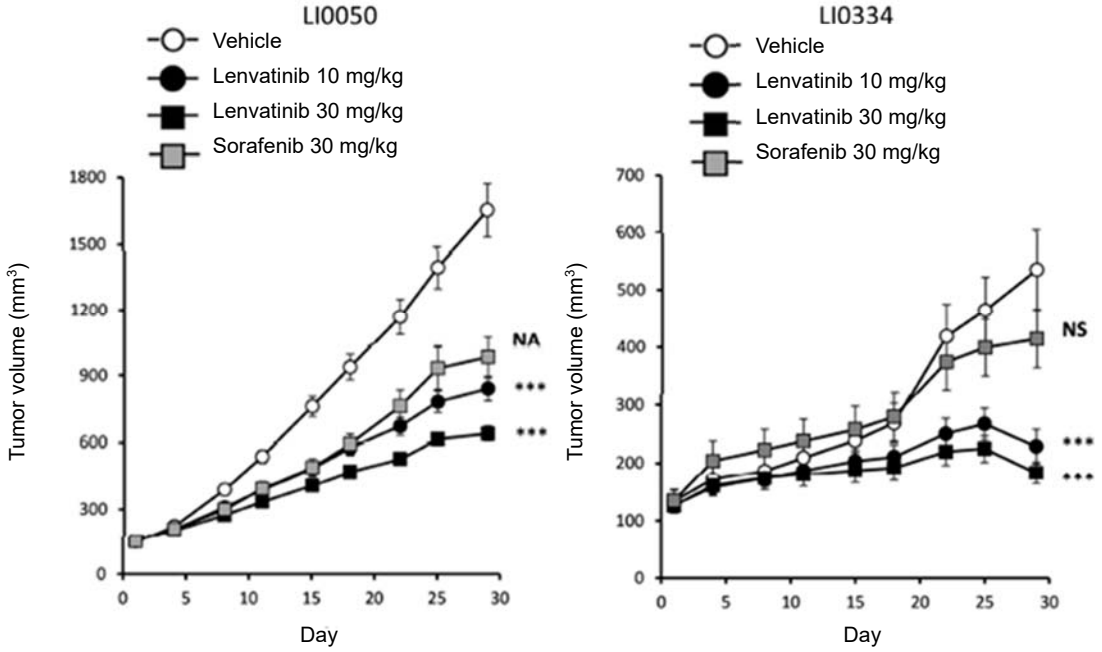

Figure 1. Tumor growth inhibitory effects of lenvatinib and sorafenib against tumor tissue fragments (LI0050 and LI0334) derived from patients with hepatocellular carcinoma

Mean ± standard error, n = 10 to 15; ***, $P < 0.001$ versus the vehicle group (Dunnett's multiple comparison test); NA, Not assessable; NS, No statistically significant difference

3.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA has concluded that the efficacy of lenvatinib is expected in the treatment of patients with hepatocellular carcinoma.

3.R.1 Efficacy of lenvatinib against hepatocellular carcinoma

The applicant's explanation about the efficacy of lenvatinib against hepatocellular carcinoma:
Taking the following points into account, the efficacy of lenvatinib against hepatocellular carcinoma is expected.

- Lenvatinib, which is a kinase inhibitor, inhibits VEGFR2-medaited signal transduction and thereby inhibits tumor angiogenesis (see "Review Report Lenvima Capsules 4 mg, Lenvima Capsules 10 mg dated January 9, 2015").

- Lenvatinib exerted the tumor growth inhibitory effect against tumor tissue fragments derived from patients with hepatocellular carcinoma [see Section 3.1.4.2].

In addition, taking the following findings into account, lenvatinib potentially has a more potent tumor growth inhibitory effect than sorafenib used in the control group in Study 304 [see Section 7.1.1.2].

- Comparison of pharmacological properties between lenvatinib and sorafenib indicates that some types of kinases (VEGFR2, etc.) are inhibited by both drugs, and others are inhibited only by either drug (lenvatinib inhibits FGFR as well) (see "Review Report Lenvima Capsules 4 mg, Lenvima Capsules 10 mg dated January 9, 2015").

- Hepatocellular carcinoma remarkably expressing FGFR1, FGFR2, FGFR3, and FGFR4 (*Cancer Res.* 2006;66:1481-90, *J Hepatol.* 2009;50:118-27, etc.) was found to have developed vascular plexus in its tumor tissue (*Expert Rev Anticancer Ther.* 2009;9:503-9). In addition, inhibition against FGF-mediated signal transduction leads to inhibition against angiogenesis [see Sections 3.1.2 and 3.1.3].

- In studies using mice transplanted with tumor tissue fragments derived from patients with hepatocellular carcinoma, the lenvatinib groups showed a statistically significant tumor growth inhibitory effect in comparison with the vehicle group, while sorafenib was not well tolerated or the sorafenib groups show any statistically significant tumor growth inhibitory effect [see Section 3.1.4.2].

- In a study using mice transplanted with tumor tissue fragments derived from a patient with hepatocellular carcinoma overexpressing FGFR1, lenvatinib exerted a more potent tumor growth inhibitory effect than sorafenib (*Oncotarget.* 2015;6:20160-76).

PMDA's view:
PMDA largely accepted the applicant's explanation. The extent of involvement of lenvatinib-inhibited kinases in tumor growth, however, has remained largely unclear, and information on this matter is considered useful in identifying patients eligible for lenvatinib treatment. Therefore, the applicant

should continue collecting information and, when new findings become available, should provide the information to healthcare professionals appropriately.

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

Although this application is intended for addition of new indication and dosages, data relating to non-clinical pharmacokinetics are considered to have been evaluated for the initial approval, and thus no new study data were submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

Since this application is intended for addition of new indication and dosages, no data relating to toxicity were submitted.

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

Although this application is intended for addition of new indication and dosages, data relating to biopharmaceutic studies and associated analytical methods are considered to have been evaluated for the initial approval, and thus no new study data were submitted.

6.1 Clinical pharmacology

Pharmacokinetics (PK) of lenvatinib in patients with cancer was investigated following the lenvatinib monotherapy.

6.1.1 Global phase III study (CTD 5.3.5.1, Study 304 [ongoing since March 2013 (data cut-off on November 13, 2016)])

An open-label, randomized, controlled study was conducted to compare the efficacy and safety between lenvatinib and sorafenib in 954 patients with systemic chemotherapy-naive unresectable hepatocellular carcinoma (468 patients included in the PK analysis). Each dosing cycle consisted of 28 days for either drug. In the lenvatinib group, patients weighing <60 kg and ≥60 kg orally received lenvatinib at 8 and 12 mg, respectively, QD; and in the sorafenib group, patients orally received sorafenib at 400 mg bis in die (BID).

As shown in Table 1, plasma lenvatinib concentrations did not clearly differ between patients weighing <60 kg and patients weighing ≥60 kg.

Table 1. Plasma lenvatinib concentrations (ng/mL)

Timepoint	Patients weighing <60 kg Lenvatinib 8 mg QD		Patients weighing ≥60 kg Lenvatinib 12 mg QD	
	n	C_{trough}	n	C_{trough}
Day 15 of Cycle 1	136	37.70 ± 25.58	299	40.83 ± 34.97
Day 1 of Cycle 2	128	36.80 ± 33.01	275	37.30 ± 28.19
Day 1 of Cycle 3	62	32.46 ± 33.83	139	40.95 ± 40.39
Day 1 of Cycle 4	65	29.74 ± 28.01	136	38.25 ± 36.82
Day 1 of Cycle 5	65	36.07 ± 40.59	129	34.02 ± 27.09
Day 1 of Cycle 6	59	38.73 ± 50.49	128	32.94 ± 25.89

Arithmetic mean ± standard deviation

6.1.2 Population pharmacokinetic analysis

6.1.2.1 Population pharmacokinetic analysis on data from global phase I/II studies

A population pharmacokinetic (PPK) analysis was performed with a nonlinear mixed effect model (software in use, NONMEM version 7.2.0) using PK data of lenvatinib (8761 timepoints in 452 subjects) obtained from foreign phase I studies (Studies E7080-A001-001, E7080-A001-002, E7080-A001-003, E7080-A001-004, E7080-A001-005, E7080-A001-006, E7080-A001-007, E7080-A001-008, E7080-E044-101, and E7080-A001-102), Japanese phase I studies (Studies E7080-J081-103 and E7080-J081-105), and global phase I/II study (Study 202). PK of lenvatinib was described in a 3-compartment model including the first order absorption process and first order elimination process.

In this analysis, AUC in patients weighing 40 to 120 kg who orally received lenvatinib at 8 or 12 mg QD was estimated. Both estimated AUC in patients weighing <60 kg and patients weighing ≥60 kg who orally received lenvatinib at 8 and 12 mg QD, respectively, were found below the AUC cut-off value in Cycle 1 at which adverse events leading to treatment discontinuation or dose reduction of lenvatinib potentially occur (2430 ng·h/mL) [see Section 6.1.3.2]. In addition, the estimated AUC (range) of lenvatinib in patients weighing 40 to 60 kg who orally received lenvatinib at 8 mg QD (1540-2050 ng·h/mL) was found comparable to that in patients weighing 60 to 120 kg who orally received lenvatinib at 12 mg QD (1410-2310 ng·h/mL).

6.1.2.2 PPK analysis on data from global phase III studies

A PPK analysis was performed with a nonlinear mixed effect model (software in use, NONMEM version 7.2.0) using PK data of lenvatinib (13,240 timepoints in 1148 subjects) obtained from foreign phase I studies (Studies E7080-A001-001, E7080-A001-002, E7080-A001-003, E7080-A001-005, E7080-A001-006, E7080-A001-008, E7080-E044-101, and E7080-A001-102), Japanese phase I studies (Studies E7080-J081-103 and E7080-J081-105), global phase I/II study (Study 202), and global phase III studies (Studies 303 and 304).

In the PPK analysis of lenvatinib submitted for the initial approval, selected covariates significant for CL/F included body weight, presence or absence of concomitant cytochrome P450 (CYP)3A inducer or inhibitor, albumin, alkaline phosphatase (ALP), and diseases (see “Review Report Lenvima Capsules 4 mg, Lenvima Capsules 10 mg dated January 9, 2015”). In this analysis, therefore, a model in which effects of the above covariates on CL/F were integrated was constructed. Using the concerned model, a cancer type (hepatocellular carcinoma and other than hepatocellular carcinoma) was investigated as potential covariate for CL/F, and was selected as a significant covariate. CL/F of lenvatinib in patients with hepatocellular carcinoma estimated by the PPK analysis was 13.2% lower than that in patients with non-hepatocellular carcinoma cancer. The applicant, however, explained that the effect of the concerned covariate on CL/F of lenvatinib was limited in consideration of the inter-individual variability (25.4%).

6.1.3 Relationship between exposure and efficacy or safety

6.1.3.1 Relationship between exposure and efficacy

Based on data from the phase II part of a global phase I/II study (Study 202), patients were divided into 3 groups according to tertiles of the exposure (AUC) of lenvatinib estimated by the PPK analysis [see

Section 6.1.2.1], and the time to progression (TTP) in each exposure group was estimated by Kaplan-Meier method. No clear relationship between the AUC and TTP was observed.

Based on data from a global phase III study (Study 304), a relationship of exposure to lenvatinib (AUC at steady state) estimated by the PPK analysis [see Section 6.1.2.2] and overall survival (OS) was investigated by a multivariate analysis. No clear relationship between AUC at steady state and OS was observed.

6.1.3.2 Relationship between exposure and safety

Based on data from the phase II part of a global phase I/II study (Study 202), a relationship of exposure to lenvatinib (AUC) estimated by the PPK analysis [see Section 6.1.2.1] and adverse events leading to treatment discontinuation or dose reduction in Cycle 1 was investigated. AUC (median) of lenvatinib in patients who experienced adverse events leading to treatment discontinuation or dose reduction of lenvatinib in Cycle 1 (2950 ng·h/mL) was higher than that in patients who did not experience such events (2050 ng·h/mL). In addition, based on a receiver operating characteristic (ROC) curve, the cut-off AUC value at which adverse events leading to treatment discontinuation or dose reduction of lenvatinib in Cycle 1 potentially occur was estimated to be 2430 ng·h/mL.

Based on data from the global phase III study (Study 304), relationships of the exposure to lenvatinib (AUC at steady state) estimated by the PPK analysis [see Section 6.1.2.2] to adverse events leading to treatment discontinuation, treatment interruption, or dose reduction of lenvatinib as well as hypertension, proteinuria, weight decreased, fatigue, vomiting, thrombocytopenia, platelet count decreased, diarrhoea, palmar-plantar erythrodysaesthesia syndrome, decreased appetite, and hepatic encephalopathy were investigated by logistic regression. The results suggested that incidences of adverse events leading to treatment interruption or dose reduction of lenvatinib as well as decreased appetite increased with increasing AUC at steady state.

6.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA has concluded that the applicant's explanation on PK of lenvatinib is acceptable.

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

The applicant submitted results from a total of 2 studies, namely, 1 global phase I/II study and 1 global phase III study provided in Table 2, as the efficacy and safety evaluation data.

Table 2. List of clinical studies on efficacy and safety

Data category	Region	Study	Phase	Study population	No. of enrollment	Outline of dosage regimen	Primary endpoint
Evaluation	Global	Study 202	I/II	Patients with unresectable hepatocellular carcinoma for which no standard therapy was available	66 (a) 20 (b) 46	(a) Phase I part, oral dose of lenvatinib 8, 12 or 16 mg QD (b) Phase II part, oral dose of lenvatinib 12 mg QD	Safety Efficacy
		Study 304	III	Patients with systemic chemotherapy-naive unresectable hepatocellular carcinoma	954 (a) 478 (b) 476	(a) Oral dose of lenvatinib 8 or 12 mg* QD (b) Oral dose of sorafenib 400 mg BID	Efficacy Safety

* 8 mg for patients weighing <60 kg and 12 mg for patients weighing ≥60 kg

The outline of each clinical study is as described below.

Major adverse events reported other than death in clinical studies are described in Section "7.2 Adverse events observed in clinical studies."

7.1 Evaluation data

7.1.1 Global studies

7.1.1.1 Global phase I/II study (CTD 5.3.5.2, Study 202 [July 2009 to August 2015])

An open-label, uncontrolled study was conducted to investigate the safety of lenvatinib in patients with unresectable hepatocellular carcinoma for which the standard therapy was not available (target sample size; 18-36 patients in the phase I part [12-18 in Arm 1,[7)] 6-18 in Arm 2[8)]], 46 patients in the phase II part[7)]). The phase I part was conducted at 2 study sites in Japan, and the phase II part was at 14 study sites in 2 countries including Japan.

The patients in Arm 1 orally received lenvatinib at 12 or 16 mg QD; patients in Arm 2 orally received lenvatinib at 8 or 12 mg QD; and patients in the phase II part orally received lenvatinib at 12 mg QD until disease progression was assessed or the discontinuation criteria were met.

The subjects enrolled in this study including 20 subjects in the phase I part (9 in Arm 1, 11 in Arm 2) and 46 subjects in the phase II part were included in the safety analysis.

In the phase I part, the dose limiting toxicity (DLT) was evaluated until Day 28 of lenvatinib administration and the tolerability was evaluated. In Arm 1, DLT occurred in 1 of 6 subjects (Grade 2 pyrexia/Grade 1 vomiting[9)] in 1 subject) in the 12 mg group and in 2 of 3 subjects (Grade 3 hepatic function disorder/Grade 3 hepatic encephalopathy and Grade 3 proteinuria in 1 subject each) in the 16 mg group. The maximum tolerated dose (MTD) of lenvatinib in Arm 1, therefore, was determined to be 12 mg QD oral dose. In Arm 2, DLT occurred in 2 of 5 subjects (Grade 3 hepatic encephalopathy and Grade 3 aspartate aminotransferase [AST] increased/Grade 3 hyperbilirubinaemia/Grade 2 blood

7) Patients with Child-Pugh liver function class A (5 or 6 points) were included.
8) Of patients with Child-Pugh liver function class B (7-9 points), patients with 7 or 8 points were included.
9) Because the number of administrations of lenvatinib was <75% of the planned number of administration during the DLT evaluation period, the events were assessed as the DLT.

creatinine increased[9)] in 1 subject each) in the 12 mg group. The MTD of lenvatinib in Arm 2, therefore, was determined to be 8 mg QD oral dose.

For the safety, no deaths during the treatment period of lenvatinib or within 30 days after the end of treatment occurred in Arm 1 in the phase I part, but such deaths occurred in 2 of 11 subjects in Arm 2 and 2 of 46 subjects in the phase II part. Causes of deaths included haematemesis and hepatic failure (1 subject each) in the phase I part and pneumonia and tumour rupture (1 subject each) in the phase II part. Of any cause, the causal relationship to lenvatinib was ruled out.

7.1.1.2 Global phase III study (CTD 5.3.5.1, Study 304 [March 2013 to November 2016])

An open-label, randomized, controlled study was conducted to compare the efficacy and safety between lenvatinib and sorafenib in patients with systemic chemotherapy-naive unresectable hepatocellular carcinoma[10)] (target sample size, approximately 940 subjects) at 183 study sites in 21 countries including Japan.

In the lenvatinib group, patients weighing <60 kg and ≥60 kg orally received lenvatinib at 8 and 12 mg, respectively, QD; and in the sorafenib group, patients orally received sorafenib at 400 mg BID until disease progression was assessed or the discontinuation criteria were met.

All of the 954 subjects (478 in the lenvatinib group, 476 in the sorafenib group) who were enrolled in this study and randomized were included in the efficacy analysis as the full analysis set (FAS). Of the FAS, 951 subjects (476 in the lenvatinib group, 475 in the sorafenib group), excluding 3 subjects who did not receive the study drug, were included in the safety analysis.

The primary endpoint in this study was OS, and 2 interim analyses were planned to evaluate the futility when the number of events reached approximately 210 and 490 (30% and 70%, respectively, of the target number of events). The final analysis was performed (when the number of events reached the target number, approximately 700) to verify non-inferiority of the lenvatinib group to the sorafenib group on the verification hypothesis that the upper limit of 95% CI of the hazard ratio of the lenvatinib group to the sorafenib group would not exceed 1.08 [see Section 7.R.2.1]. In addition, when non-inferiority of the lenvatinib group to the sorafenib group was indicated, superiority of the lenvatinib group to the sorafenib group was investigated by stratified log-rank test.

Based on results from the first and second interim analyses performed on [redacted], 20[redacted] and [redacted], 20[redacted], respectively, the independent data monitoring committee (IDMC) recommended continuation of this study. The final analysis was performed on OS with data cut-off on November 13, 2016. Results on OS from the final analysis and Kaplan-Meier curve are as shown in Table 3 and Figure 2, respectively, verifying non-inferiority of the lenvatinib group to the sorafenib group. On the other hand, the superiority of the lenvatinib group to the sorafenib group was not indicated.

[10)] Patients with Child-Pugh liver function class A (5 or 6 points) for whom local therapy was not indicated were included.

Table 3. Results on OS from the final analysis (FAS, data cut-off on November 13, 2016)

	Lenvatinib	Sorafenib
Number of subjects	478	476
Number of events (%)	351 (73.4)	350 (73.5)
Median [95% CI] (months)	13.6 [12.1, 14.9]	12.3 [10.4, 13.9]
Hazard ratio [95% CI]*	0.92 [0.79, 1.06]	

* Stratified Cox regression using region (Asia Pacific region, others), macroscopic portal vein invasion or extrahepatic metastases (presence, absence), Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0, 1), and body weight (<60 kg, ≥60 kg) as stratification factors

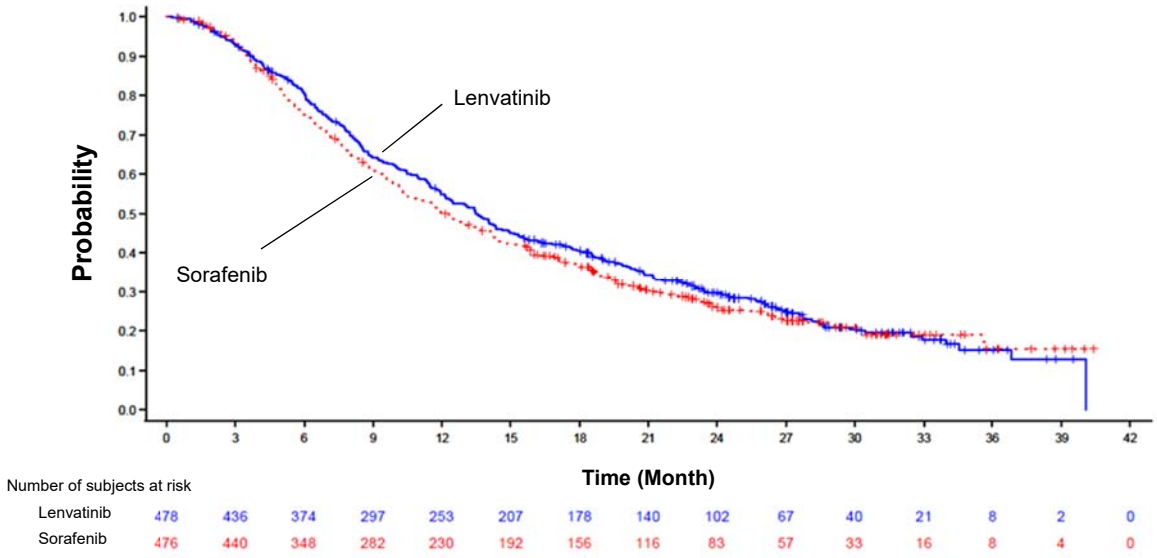

Figure 2. Kaplan-Meier curve on OS at the time of the final analysis (FAS, data cut-off on November 13, 2016)

For the safety, deaths during the treatment period of the study drug or within 30 days after the end of treatment occurred in 63 of 476 subjects (13.2%) in the lenvatinib group and 36 of 475 subjects (7.6%) in the sorafenib group. Causes of deaths except for deaths due to disease progression (11 subjects in the lenvatinib group, 14 subjects in the sorafenib group) included hepatic failure (7 subjects), sepsis (3 subjects), hepatic encephalopathy, general physical health deterioration, cerebrovascular accident, respiratory failure, cerebral haemorrhage, and death (2 subjects each), and cardiopulmonary failure, acute hepatic failure, chronic hepatic failure, renal impairment, cholangitis, disseminated intravascular coagulation/sepsis, dyspnoea, portal vein thrombosis, pneumonia aspiration, pneumonia aspiration/multiple organ dysfunction syndrome/acute respiratory failure, portal vein thrombosis/coma hepatic, intestinal haemorrhage, sudden death, pulmonary embolism, bile duct obstruction/hepatic failure/multiple organ dysfunction syndrome/pancreatitis acute, pulmonary infarction, coma hepatic, cerebral haemorrhage/upper gastrointestinal haemorrhage/respiratory failure, organ failure, upper gastrointestinal haemorrhage, hepatic failure/sepsis, metastases to central nervous system, liver carcinoma ruptured, hepatic cirrhosis, circulatory collapse, hepatic failure/peritonitis bacterial, tumour haemorrhage, myocardial infarction, cachexia, and Escherichia sepsis (1 subject each) in the lenvatinib group; and respiratory failure (3 subjects), hepatic failure, upper gastrointestinal haemorrhage, and sudden death (2 subjects each), and renal impairment/hepatic function abnormal, septic shock, sepsis, general physical health deterioration, traumatic haematoma/subarachnoid haemorrhage, tumour haemorrhage, ascites, ischaemic stroke, oesophageal varices haemorrhage, renal impairment, multiple

organ dysfunction syndrome, liver carcinoma ruptured and acute respiratory failure (1 subject each) in the sorafenib group. Of these, a causal relationship to the study drug could not be ruled out for hepatic failure in 3 subjects, sepsis, cerebrovascular accident and cerebral haemorrhage (2 subjects each), cerebral haemorrhage/upper gastrointestinal haemorrhage/respiratory failure, circulatory collapse, myocardial infarction, and respiratory failure (1 subject each) in the lenvatinib group and respiratory failure, sudden death, and ischaemic stroke (1 subject each) in the sorafenib group.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA concluded that, among the submitted evaluation data, the most important clinical study for evaluating the efficacy and safety of lenvatinib was the global phase III study (Study 304), which was intended to investigate the efficacy and safety of lenvatinib in patients with systemic chemotherapy-naive unresectable hepatocellular carcinoma. Thus, PMDA decided to evaluate the submitted data, focusing on the concerned study. PMDA decided to investigate the efficacy in Japanese patients from a viewpoint of consistency between the overall population and Japanese population in Study 304 in accordance with the "Basic Principles on Global Clinical Trials" (PFSB/ELD No. 0928010 dated September 28, 2007), "Basic Principles on Global Clinical Trials (Reference Cases)" (Administrative Notice dated September 5, 2012).

7.R.2 Efficacy

Based on the following review, PMDA has concluded that the efficacy of lenvatinib in patients with systemic chemotherapy-naive unresectable hepatocellular carcinoma was demonstrated.

7.R.2.1 Use of control group and verification hypothesis

The applicant's explanation about the reason for selecting the control group in Study 304 and verification hypothesis:

At the time when Study 304 was planned, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Hepatobiliary Cancers (NCCN guidelines) (v. 2.2012) recommended use of sorafenib in patients with systemic chemotherapy-naive unresectable hepatocellular carcinoma based on results from foreign phase III studies (the SHARP study [*N Engl J Med.* 2008;359:378-90] and the Asia-Pacific study [*Lancet Oncol.* 2009;10:25-34]) that showed statistically significant prolongation of OS with sorafenib in comparison with the placebo in such patients, and therefore sorafenib was chosen as the control drug in Study 304.

In addition, at the time when Study 304 was planned, the applicant considered it possible to demonstrate clinical usefulness of lenvatinib even if only its non-inferiority to sorafenib was verified, for the following reasons: (a) Sorafenib was only one approved drug in Japan for in patients with systemic chemotherapy unresectable hepatocellular carcinoma, and drug options for systemic chemotherapy in such patients were extremely limited; and (b) the safety profile differed between lenvatinib and sorafenib. In Study 304, therefore, hypothesis to verify non-inferiority of the lenvatinib group to the sorafenib group was used. For the non-inferiority margin, 1.08 of the hazard ratio of the lenvatinib group to the sorafenib group was selected in consideration of the following review.

- The hazard ratio [95% CI] of OS in the sorafenib group to that in the placebo group was determined to be 0.6865 [0.5709, 0.8255] based on the hazard ratios [95% CI] in the SHARP and Asia-Pacific studies (0.69 [0.55, 0.87] and 0.68 [0.50, 0.93], respectively) by meta-analysis (*Stat Med.* 1998;17:2815-34, Erratum 2004).

- To ensure that lenvatinib could maintain 60% of the effect of sorafenib ($\delta = 0.60$), the non-inferiority margin was determined using the above hazard ratio [95% CI] of OS in the sorafenib group to that in the placebo group by the Rothmann's 95% CI lower limit-based method for the log hazard ratio (*Stat Med.* 2003;22:239-64).

PMDA accepted the applicant's explanation.

7.R.2.3 Efficacy endpoints and evaluation results

In Study 304, OS was selected as the primary endpoint, and non-inferiority of the lenvatinib group to the sorafenib group was verified [see Section 7.1.1.2].

Results on OS from the final analysis and Kaplan-Meier curve in the Japanese population in Study 304 are as shown in Table 4 and Figure 3, respectively.

Table 4. Results on OS from the final analysis in the Japanese population (data cut-off on November 13, 2016)

	Lenvatinib	Sorafenib
Number of subjects	81	87
Number of deaths (%)	60 (74.1)	70 (80.5)
Median [95% CI] (months)	17.6 [12.2, 23.0]	17.8 [11.9, 19.5]
Hazard ratio [95% CI]*	0.90 [0.62, 1.29]	

* Stratified Cox regression using macroscopic portal vein invasion or extrahepatic metastases (presence, absence), ECOG PS (0, 1), and body weight (<60 kg, ≥60 kg) as stratification factors

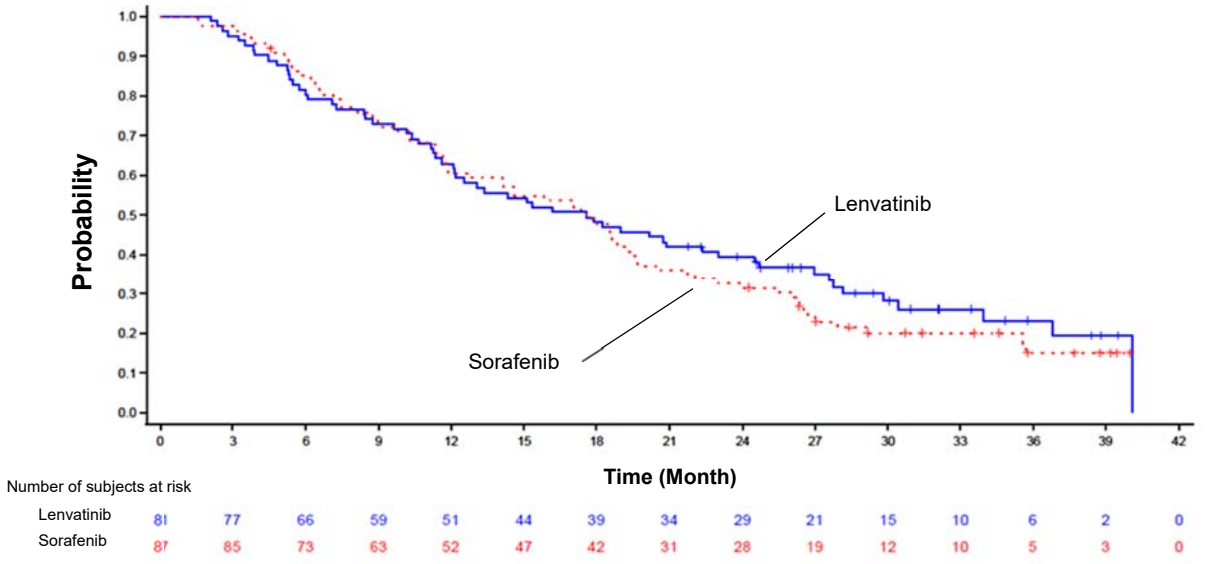

Figure 3. Kaplan-Meier curve on OS at the time of the final analysis in the Japanese population (Japanese population, data cut-off on November 13, 2016)

PMDA's view:
It is appropriate to select OS as the primary endpoint in Study 304 in patients with systemic chemotherapy-naive unresectable hepatocellular carcinoma. In consideration of the following points, the efficacy of lenvatinib in the concerned patients was demonstrated:

- For the OS, the primary endpoint in Study 304, non-inferiority of the lenvatinib group to the sorafenib group was verified.

- Numbers of Japanese patients enrolled and events observed in Study 304 were limited, and therefore there is a limitation in evaluating the efficacy of lenvatinib in Japanese patients, but the above results in the Japanese population did not show any clearly different trend from those in the overall population.

7.R.3 Safety [see Section "7.2 Adverse events observed in clinical studies" for adverse events]
As a result of the reviews described below, PMDA considers that special caution is required in the treatment with lenvatinib in patients with unresectable hepatocellular carcinoma for the adverse events for which caution was judged to be required at the time of initial approval for unresectable thyroid cancer (hypertension/hypertensive crisis, infections, renal disorder, haemorrhage-related events, palmar-plantar erythrodysaesthesia syndrome, haematotoxicity, liver disorder, arrhythmia, cardiac function disturbance, hypocalcaemia, thromboembolism, gastrointestinal perforation and gastrointestinal fistulae, posterior reversible encephalopathy syndrome, wound healing delayed, and blood thyroid stimulating hormone increased) (see "Review Report Lenvima Capsules 4 mg, Lenvima Capsules 10 mg dated January 9, 2015"). Caution should be used for these adverse events during treatment with lenvatinib as practiced in its use for the approved indication of thyroid cancer.

PMDA further concluded that, although the treatment requires caution with the adverse events, lenvatinib is tolerable in patients with hepatocellular carcinoma as well, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy by appropriate means of adverse event monitoring and control, treatment interruption, etc.

7.R.3.1 Safety profile
Based on the safety information obtained in Study 304, the applicant explained the safety profile of lenvatinib as follows:
The outline of the safety in Study 304 is as shown in Table 5.

Table 5. Outline of safety (Study 304)

	Number of subjects (%)	
	Lenvatinib n = 476	Sorafenib n = 475
All adverse events	470 (98.7)	472 (99.4)
Grade ≥3 adverse events	359 (75.4)	318 (66.9)
Adverse events resulting in death	63 (13.2)	36 (7.6)
Serious adverse events	207 (43.5)	144 (30.3)
Adverse events leading to treatment discontinuation	94 (19.7)	69 (14.5)
Adverse events leading to treatment interruption	248 (52.1)	192 (40.4)
Adverse events leading to dose reduction	184 (38.7)	185 (38.9)

Adverse events of all Grades of which the incidence was ≥5% higher in the lenvatinib group than in the sorafenib group included hypertension (199 subjects [41.8%] in the lenvatinib group, 145 subjects [30.5%] in the sorafenib group), decreased appetite (163 subjects [34.2%], 127 subjects [26.7%]), weight decreased (149 subjects [31.3%], 107 subjects [22.5%]), proteinuria (117 subjects [24.6%], 54 subjects [11.4%]), platelet count decreased (87 subjects [18.3%], 59 subjects [12.4%]), hypothyroidism (80 subjects [16.8%], 8 subjects [1.7%]), vomiting (79 subjects [16.6%], 36 subjects [7.6%]), constipation (76 subjects [16.0%], 52 subjects [10.9%]), ascites (69 subjects [14.5%], 45 subjects [9.5%]), oedema peripheral (66 subjects [13.9%], 33 subjects [6.9%]), neutrophil count decreased (41 subjects [8.6%], 11 subjects [2.3%]), hepatic encephalopathy (38 subjects [8.0%], 9 subjects [1.9%]), and dry mouth (32 subjects [6.7%], 8 subjects [1.7%]). Grade ≥3 adverse events of which the incidence was ≥2% higher in the lenvatinib group than in the sorafenib group included hypertension (111 subjects [23.3%], 68 subjects [14.3%]), weight decreased (36 subjects [7.6%], 14 subjects [2.9%]), proteinuria (27 subjects [5.7%], 8 subjects [1.7%]), platelet count decreased (26 subjects [5.5%], 16 subjects [3.4%]), hepatic encephalopathy (23 subjects [4.8%], 7 subjects [1.5%]), and decreased appetite (22 subjects [4.6%], 6 subjects [1.3%]). Serious adverse events of which the incidence was ≥2% higher in the lenvatinib group than in the sorafenib group included hepatic encephalopathy (21 subjects [4.4%], 3 subjects [0.6%]). There were no adverse events leading to treatment discontinuation of which the incidence was ≥2% higher in the lenvatinib group than in the sorafenib group.

The applicant's explanation about the difference in the safety profile of lenvatinib between patients with hepatocellular carcinoma and patients with thyroid cancer, the approved indication:
Table 6 shows comparison of adverse events in the lenvatinib group in Study 304 and those in the lenvatinib group in a global phase III study (Study E7080-G000-303 [Study 303]) in patients with differentiated thyroid cancer who orally received lenvatinib at 24 mg QD.

Table 6. Outline of safety in patients with hepatocellular carcinoma and patients with thyroid cancer

	Number of subjects (%)	
	Hepatocellular carcinoma n = 476	Thyroid cancer n = 261
All adverse events	470 (98.7)	260 (99.6)
Grade ≥3 adverse events	359 (75.4)	236 (90.4)
Adverse events resulting in death	63 (13.2)	26 (10.0)
Serious adverse events	207 (43.5)	167 (64.0)
Adverse events leading to treatment discontinuation	94 (19.7)	60 (23.0)
Adverse events leading to treatment interruption	248 (52.1)	224 (85.8)
Adverse events leading to dose reduction	184 (38.7)	184 (70.5)

Adverse events of all Grades of which the incidence was ≥5% higher in patients with hepatocellular carcinoma than in patients with thyroid cancer included platelet count decreased (87 patients with hepatocellular carcinoma [18.3%], 17 patients with thyroid cancer [6.5%]), hypothyroidism (80 patients [16.8%], 14 patients [5.4%]), blood bilirubin increased (72 patients [15.1%], 8 patients [3.1%]), ascites (69 patients [14.5%], 1 patient [0.4%]), AST increased (65 patients [13.7%], 18 patients [6.9%]), neutrophil count decreased (41 patients [8.6%], 3 patients [1.1%]), abdominal distension (39 patients [8.2%], 7 patients [2.7%]), hepatic encephalopathy (38 patients [8.0%], 0 patients), and γ-glutamyl transferase (γ-GTP) increased (37 patients [7.8%], 5 patients [1.9%]). Similarly, Grade ≥3 adverse events of which the incidence was ≥5% higher in patients with hepatocellular carcinoma than in patients with thyroid cancer included blood bilirubin increased (31 patients [6.5%], 1 patient [0.4%]) and platelet count decreased (26 patients [5.5%], 1 patient [0.4%]). Serious adverse events of which the incidence was ≥2% higher in patients with hepatocellular carcinoma than in patients with thyroid cancer included hepatic encephalopathy (21 patients [4.4%], 0 patients), hepatic failure (14 patients [2.9%], 1 patient [0.4%]), and ascites (12 patients [2.5%], 0 patients). Similarly, there were no adverse events resulting in death, adverse events leading to treatment discontinuation, treatment interruption, or dose reduction of which the incidence was ≥5% higher in patients with hepatocellular carcinoma than in patients with thyroid cancer.

PMDA's view:
Most of the adverse events of which the incidence was higher in the lenvatinib group than in the sorafenib group in Study 304 were known events for lenvatinib. In addition, although there were some adverse events of which the incidence was higher in patients with hepatocellular carcinoma than in patients with thyroid cancer as shown above, any event was considered attributable to the primary disease, and the incidence of serious adverse events was not increased in patients with hepatocellular carcinoma.

Based on the above, PMDA has concluded that lenvatinib is tolerable in patients with hepatocellular carcinoma as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy by appropriate means of adverse event monitoring and control, treatment interruption, etc.

7.R.3.2 Differences in safety between Japanese and non-Japanese patients

The applicant's explanation about differences in safety between Japanese and non-Japanese patients:
Table 7 shows the outline of safety in Japanese and non-Japanese patients in the lenvatinib group in Study 304.

Table 7. Outline of safety (Study 304)

	Number of subjects (%)	
	Japanese patients n = 81	Non-Japanese patients n = 395
All adverse events	81 (100)	389 (98.5)
Grade ≥3 adverse events	63 (77.8)	296 (74.9)
Adverse events resulting in death	5 (6.2)	58 (14.7)
Serious adverse events	31 (38.3)	176 (44.6)
Adverse events leading to treatment discontinuation	15 (18.5)	79 (20.0)
Adverse events leading to treatment interruption	52 (64.2)	196 (49.6)
Adverse events leading to dose reduction	50 (61.7)	134 (33.9)

Adverse events of all Grades of which the incidence was ≥20% higher in Japanese patients than in non-Japanese patients included palmar-plantar erythrodysaesthesia syndrome (42 Japanese patients [51.9%], 86 non-Japanese patients [21.8%]), proteinuria (38 patients [46.9%], 79 patients [20.0%]), dysphonia (35 patients [43.2%], 78 patients [19.7%]), and hypothyroidism (33 patients [40.7%], 47 patients [11.9%]). Grade ≥3 adverse events of which the incidence was ≥5% higher in Japanese patients than in non-Japanese patients included hypertension (28 patients [34.6%], 83 patients [21.0%]), decreased appetite (8 patients [9.9%], 14 patients [3.5%]), neutrophil count decreased (6 patients [7.4%], 9 patients [2.3%]), palmar-plantar erythrodysaesthesia syndrome (6 patients [7.4%], 8 patients [2.0%]), and hepatic function abnormal (6 patients [7.4%], 2 patients [0.5%]). Adverse events leading to treatment interruption of which the incidence was ≥5% higher in Japanese patients than in non-Japanese patients included decreased appetite (11 patients [13.6%], 13 patients [3.3%]) and palmar-plantar erythrodysaesthesia syndrome (7 patients [8.6%], 7 patients [1.8%]). Adverse events leading to dose reduction of which the incidence was ≥5% higher in Japanese patients than in non-Japanese patients included decreased appetite (12 patients [14.8%], 14 patients [3.5%]), palmar-plantar erythrodysaesthesia syndrome (8 patients [9.9%], 15 patients [3.8%]), and malaise (5 patients [6.2%], 0 patients). There were no adverse events resulting in death, serious adverse events, or adverse events leading to treatment discontinuation of which the incidence was ≥5% higher in Japanese patients than in non-Japanese patients.

PMDA's view:
Only a limited number of Japanese patients with hepatocellular carcinoma have received lenvatinib, and thus there is a limitation in comparing the safety between Japanese and non-Japanese patients strictly. However, based on the following results in Study 304, lenvatinib is tolerable in Japanese patients with hepatocellular carcinoma as well.

- Any of the adverse events of which the incidence was higher in Japanese patients than in non-Japanese patients was known events for lenvatinib.

- No clear differences were observed in incidence of adverse events resulting in death, serious adverse events, or adverse events leading to treatment discontinuation between Japanese and non-Japanese patients, and these adverse events were controlled with dose reduction or treatment interruption.

In the following section, PMDA reviews the safety, focusing on hepatic encephalopathy, an event related to the primary disease of which incidence was particularly higher in patients with hepatocellular carcinoma than in patients with thyroid cancer.

7.R.3.3 Hepatic encephalopathy

The applicant's explanation about hepatic encephalopathy during the treatment with lenvatinib:
Adverse events reported as preferred terms (PTs) of Medical Dictionary for Regulatory Activities Japanese version (MedDRA) ver. 19.1 corresponding to "hepatic encephalopathy" were tabulated as events related to hepatic encephalopathy.

Table 8 shows adverse events related to hepatic encephalopathy in Study 304.

Table 8. Adverse events related to hepatic encephalopathy (Study 304)

PT (MedDRA ver. 19.1)	Number of subjects (%)			
	Lenvatinib n = 476		Sorafenib n = 475	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events related to hepatic encephalopathy	40 (8.4)	26 (5.5)	13 (2.7)	9 (1.9)
Hepatic encephalopathy	38 (8.0)	23 (4.8)	9 (1.9)	7 (1.5)
Coma hepatic	3 (0.6)	3 (0.6)	1 (0.2)	1 (0.2)
Encephalopathy	1 (0.2)	1 (0.2)	2 (0.4)	1 (0.2)
Metabolic encephalopathy	0	0	1 (0.2)	0

Fatal hepatic encephalopathy-related events occurred in 4 subjects in the lenvatinib group (0.8%, hepatic encephalopathy and coma hepatic in 2 subjects each) in Study 304 (no such events occurred in the sorafenib group), and a causal relationship to the study drug was ruled out for all events. Serious hepatic encephalopathy-related events occurred in 24 subjects in the lenvatinib group (5.0%, hepatic encephalopathy in 21 subjects, coma hepatic in 3 subjects) and 5 subjects in the sorafenib group (1.1%, hepatic encephalopathy in 3 subjects, coma hepatic and encephalopathy in 1 subject each). Of these, a causal relationship to the study drug could not be ruled out in 10 subjects in the lenvatinib group (hepatic encephalopathy in 9 subjects, coma hepatic in 1 subject) and in 1 subject in the sorafenib group (hepatic encephalopathy in 1 subject). Hepatic encephalopathy-related events leading to treatment discontinuation occurred in 8 subjects (1.7%, hepatic encephalopathy in 7 subjects, encephalopathy/coma hepatic in 1 subject) in the lenvatinib group and in 1 subject (0.2%, encephalopathy in 1 subject) in the sorafenib group. Of these, a causal relationship to the study drug could not be ruled out in 3 subjects (hepatic encephalopathy in 3 subjects) in the lenvatinib group. Hepatic encephalopathy-related events leading to treatment interruption occurred in 16 subjects (3.4%, hepatic encephalopathy in 15 subjects, coma hepatic in 1 subject) in the lenvatinib group and in 4 subjects (0.8%, hepatic encephalopathy in 3 subjects, metabolic encephalopathy in 1 subject) in the sorafenib group. Of these, a causal relationship to the study drug could not be ruled out in 10 subjects (hepatic encephalopathy in 9 subjects, coma hepatic in 1 subject) in the lenvatinib group and in 3 subjects (hepatic encephalopathy in 2 subjects, metabolic encephalopathy in 1 subject) in the sorafenib group. Hepatic encephalopathy-related events leading to dose reduction occurred in 10 subjects (2.1%, hepatic encephalopathy in 10 subjects) in the lenvatinib group and in 1 subject (0.2%, hepatic encephalopathy in 1 subject) in the sorafenib group. Of these, a causal relationship to the study drug could not be ruled out in 9 subjects (hepatic encephalopathy in 9 subjects) in the lenvatinib group.

PMDA's view:
Hepatic encephalopathy potentially occurred due to the primary disease, taking into account that (a) no such events occurred in Study 303; and (b) the related events occurred in both lenvatinib and sorafenib groups in Study 304 [see Section 7.R.3.1]. In consideration that the incidence of hepatic encephalopathy was higher in the lenvatinib group than in the sorafenib group in Study 304, however, attention should be paid to hepatic encephalopathy during treatment with lenvatinib in patients with hepatocellular carcinoma. Therefore, the applicant should appropriately provide information on the incidence of hepatic encephalopathy in clinical studies to healthcare professionals via the package insert, etc.

7.R.4 Clinical positioning and indication

The proposed indication of lenvatinib was "unresectable hepatocellular carcinoma." The following cautions were proposed for the "Precautions for Indications" section.

- The efficacy and safety of lenvatinib have not been established in patients with hepatocellular carcinoma for whom local therapies (percutaneous ethanol injection, radiofrequency ablation, microwave coagulation, hepatic artery embolization/transcatheter arterial chemoembolization [TACE], etc.) are indicated.

- The efficacy and safety of lenvatinib have not been established in adjuvant chemotherapy after resection and local therapies for hepatocellular carcinoma.

- For the treatment of hepatocellular carcinoma, eligible patients should be selected based on the severity of hepatic impairment, eligibility for local therapies, history of systemic chemotherapy, etc., which are detailed in the "Clinical Studies" section.

Based on the review in Sections "7.R.2 Efficacy" and "7.R.3 Safety" as well as the following sections, PMDA has concluded that lenvatinib should be indicated for "unresectable hepatocellular carcinoma," with the following cautionary statements in the "Precautions for Indications" section.

- The efficacy and safety of lenvatinib have not been established in patients with hepatocellular carcinoma for whom local therapies (percutaneous ethanol injection, radiofrequency ablation, microwave coagulation, hepatic artery embolization/TACE, radiation, etc.) are indicated.

- Eligible patients should be selected based on a thorough understanding of the efficacy and safety of lenvatinib as well as the characteristics of patients enrolled in the clinical studies, e.g., severity of hepatic impairment, described in the "Clinical Studies" section.

7.R.4.1 Patients to be treated with lenvatinib

Clinical practice guidelines in Japan, the Clinical Practice Guidelines for Hepatocellular Carcinoma 2017 edited by the Japan Society of Hepatology (JSH HCC Guidelines 2017), describes lenvatinib as shown below. At the time of this review, foreign clinical practice guidelines, US National Cancer

Institute's Physician Data Query (NCI-PDQ) (version dated January 31, 2017), and internationally known oncology textbooks did not mention lenvatinib in the treatment of hepatocellular carcinoma.

- Because results from Study 304 demonstrated non-inferiority of lenvatinib to sorafenib, lenvatinib will be a first-line drug in the treatment of hepatocellular carcinoma.

The applicant's explanation about clinical positioning and indication of lenvatinib:
Lenvatinib is considered to be positioned as a therapeutic option for patients with systemic chemotherapy-naive unresectable hepatocellular carcinoma, in whom the clinical usefulness of lenvatinib has been demonstrated in Study 304. Accordingly, the proposed indication of lenvatinib was determined to be "unresectable hepatocellular carcinoma" with the following measures taken.

- The Clinical Studies section in the package insert will state that Study 304 included patients with systemic chemotherapy-naïve Child-Pugh liver function class A for whom local therapy was not indicated.

- The "Precautions for Indications" section will note the following:
  - For the treatment of hepatocellular carcinoma, eligible patients should be selected based on the severity of hepatic impairment, eligibility for local therapies, history of systemic chemotherapy, etc., which are detailed in the "Clinical Studies" section.
  - The efficacy and safety of lenvatinib have not been established in adjuvant chemotherapy after resection and local therapies for hepatocellular carcinoma.
  - The efficacy and safety of lenvatinib have not been established in patients with hepatocellular carcinoma for whom local therapies (percutaneous ethanol injection, radiofrequency ablation, microwave coagulation, hepatic artery embolization/TACE, etc.) are indicated.

In addition, for patients with hepatocellular carcinoma, either lenvatinib or sorafenib can be selected in consideration of the following points.

- While treatment with sorafenib is frequently interrupted due to severe adverse drug reactions of palmar-plantar erythrodysaesthesia syndrome, discontinuation of treatment with lenvatinib due to palmar-plantar erythrodysaesthesia syndrome was not reported at least in Study 202 or 304, indicating that the safety profile differs between lenvatinib and sorafenib [see Section 7.2].

- While sorafenib is orally administered at 400 mg BID, lenvatinib is orally administered at 8 or 12 mg QD, facilitating patients to adhere to the treatment in comparison with sorafenib.

PMDA's view:
PMDA largely accepted the applicant's explanation and has concluded that lenvatinib should be indicated for "unresectable hepatocellular carcinoma" as proposed.

One of the cautionary statements, "The efficacy and safety of lenvatinib have not been established in adjuvant chemotherapy after resection and local therapies for hepatocellular carcinoma." specified in

the proposed “Precautions for Indications” section, is considered unnecessary, because adjuvant chemotherapy after resection and local therapies for hepatocellular carcinoma is not recommended as the standard therapy in Japanese or foreign clinical practice guidelines.

Based on the above, PMDA has concluded that the cautions should be modified as shown below to be included in the “Precautions for Indications” section.

- The efficacy and safety of lenvatinib have not been established in patients with hepatocellular carcinoma for whom local therapies (percutaneous ethanol injection, radiofrequency ablation, microwave coagulation, hepatic artery embolization/TACE, radiation, etc.) are indicated.

- Eligible patients should be selected based on a thorough understanding of the efficacy and safety of lenvatinib as well as the characteristics of patients enrolled in the clinical studies, e.g., severity of hepatic impairment, described in the “Clinical Studies” section.

7.R.5 Dosage and administration

The proposed dosage and administration was “The usual adult dosage is determined according to the body weight. The following dosage of lenvatinib is administered orally once daily; 12 mg for patients weighing ≥60 kg or 8 mg for patients weighing <60 kg. The dose may be reduced according to the patient’s condition.” The following cautionary statements were presented in the “Precautions for Dosage and Administration” section.

- The efficacy and safety of concomitant use of lenvatinib with the other antineoplastic drugs have not been established.

- It has been reported that the blood lenvatinib concentration increases in patients with severe hepatic impairment. The dose reduction should be considered for such patients, and patients should be carefully monitored with special attention to adverse events.

- The clinical study has confirmed that the maximum tolerated dose in patients with hepatocellular carcinoma who have moderate hepatic impairment (Child-Pugh Class B) is 8 mg once daily. These patients may be treated with the reduced dose under careful vigilance for adverse events.

- The efficacy and safety of concomitant use of lenvatinib with local therapies for hepatocellular carcinoma have not been established.

- Criteria for dose reduction, treatment interruption, and treatment discontinuation at the occurrence of adverse drug reactions

Based on the review in Sections “7.R.2 Efficacy” and “7.R.3 Safety” as well as the following sections, PMDA has concluded that the following statements should be included in the “Precautions for Dosage and Administration” section and the dosage and administration of lenvatinib should be “The usual adult dosage is determined according to the body weight; 12 mg for patients weighing ≥60 kg or 8 mg for

patients weighing <60 kg, administered orally once daily. The dose may be reduced according to the patient's condition."

- The efficacy and safety of concomitant use of lenvatinib with the other antineoplastic drugs have not been established.

- It has been reported that the blood lenvatinib concentration increases in patients with severe hepatic impairment. The dose reduction should be considered for such patients, and patients should be carefully monitored with special attention to adverse events.

- The clinical study has confirmed that the maximum tolerated dose in patients with hepatocellular carcinoma who have moderate hepatic impairment (Child-Pugh score 7-8) is 8 mg once daily. These patients may be treated with the reduced dose under careful vigilance for adverse events.

- Criteria for dose reduction, treatment interruption, and treatment discontinuation at the occurrence of adverse drug reactions

7.R.5.1 Dosage and administration of lenvatinib for patients with hepatocellular carcinoma

The applicant's explanation about rationale for selecting the dosage and administration of lenvatinib for patients with hepatocellular carcinoma:

Results from Arm 1 in the phase I part in the global phase I/II study (Study 202) indicated that MTD of lenvatinib in patients with Child-Pugh liver function class A was 12 mg [see Section 7.1.1.1]. In the phase II part, therefore, lenvatinib was orally administered at 12 mg QD. As a result, treatment discontinuation or dose reduction of lenvatinib was required in approximately half of the patients (22 of 46 subjects) due to adverse events that occurred during Cycle 1 (each cycle consisting of 28 days). Based on the above results and results from the PPK analysis on data from the global phase I/II study [see Section 6.1.2.1], the following dosage regimen of lenvatinib for Study 304 was selected: By body weight, 12 mg QD oral dose for patients weighing ≥60 kg and 8 mg QD oral dose for patients weighing <60 kg. In this study, clinical usefulness of lenvatinib was demonstrated. Tables 9 and 10 show results on OS and safety by body weight, respectively. Although the dosage regimen of lenvatinib was selected according to the body weight, no clear differences were observed in data on the efficacy and safety of lenvatinib by body weight.

Table 9. Data on the efficacy by body weight
(results from analysis on OS in Study 304, FAS, data cut-off on November 13, 2016)

Body weight	Lenvatinib		Sorafenib		Hazard ratio [95% CI]*
	Number of subjects	Median [95% CI] (months)	Number of subjects	Median [95% CI] (months)	
<60 kg	153	13.4 [10.5, 15.7]	146	10.3 [8.7, 15.9]	0.85 [0.65, 1.11]
≥60 kg	325	13.7 [12.0, 15.6]	330	12.5 [11.1, 14.2]	0.95 [0.79, 1.14]

* Stratified Cox regression using region (Asia Pacific region, others), macroscopic portal vein invasion or extrahepatic metastases (presence, absence), and ECOG PS (0, 1) as stratification factors

Table 10. Data on the safety by body weight (Study 304)

	Number of subjects (%)		
	Lenvatinib (body weight <60 kg) n = 151	Lenvatinib (body weight ≥60 kg)* n = 325	Sorafenib n = 475
All adverse events	151 (100)	319 (98.2)	472 (99.4)
Grade ≥3 adverse events	100 (66.2)	259 (79.7)	318 (66.9)
Adverse events resulting in death	14 (9.3)	49 (15.1)	36 (7.6)
Serious adverse events	58 (38.4)	149 (45.8)	144 (30.3)
Adverse events leading to treatment discontinuation	33 (21.9)	61 (18.8)	69 (14.5)
Adverse events leading to treatment interruption	72 (47.7)	176 (54.2)	192 (40.4)
Adverse events leading to dose reduction	43 (28.5)	141 (43.4)	185 (38.9)

* Including 2 subjects who weighed <60 kg but received 12 mg

The applicant proposed the Dosage and Administration and Precautions for Dosage and Administration sections as shown below, considering, in addition to the above, that (a) results from the phase I part in Study 202 revealed that the MTD of lenvatinib in patients with Child-Pugh liver function class B (7 or 8 points) was 8 mg; and (b) there are no clinical study results on clinical usefulness of concomitant use of lenvatinib with the other antineoplastic drugs and local therapies, and thus caution should be given to healthcare professionals that such concomitant use is not recommended.

Dosage and Administration

The usual adult dosage is determined according to the body weight. The following dosage of lenvatinib is administered orally once daily; 12 mg for patients weighing ≥60 kg or 8 mg for patients weighing <60 kg. The dose may be reduced according to the patient's condition.

Precautions for Dosage and Administration

- The efficacy and safety of concomitant use of lenvatinib with the other antineoplastic drugs have not been established.

- It has been reported that the blood lenvatinib concentration increases in patients with severe hepatic impairment. The dose reduction should be considered for such patients, and patients should be carefully monitored with special attention to adverse events.

- The clinical study has confirmed that the maximum tolerated dose in patients with hepatocellular carcinoma who have moderate hepatic impairment (Child-Pugh Class B) is 8 mg once daily. These patients may be treated with the reduced dose under careful vigilance for adverse events.

- The efficacy and safety of concomitant use of lenvatinib with local therapies for hepatocellular carcinoma have not been established.

PMDA's view:

PMDA largely accepted the applicant's above explanation and has concluded that the proposed dosage and administration of lenvatinib should be modified as follows: "The usual adult dosage is determined according to the body weight; 12 mg for patients weighing ≥60 kg or 8 mg for patients weighing <60 kg, administered orally once daily. The dose may be reduced according to the patient's condition."

One of the cautionary statements originally presented in the proposed "Precautions for Dosage and Administration" section, "the efficacy and safety of concomitant use of lenvatinib with local therapies have not been established" will be appeared in the "Precautions for Indications" section [see Section 7.R.4]. Thus there is little need of presenting the concerned statement in multiple sections.

Based on the above, PMDA has concluded that the statements should be modified as below to be presented in the "Precautions for Dosage and Administration" section.

- The efficacy and safety of concomitant use of lenvatinib with the other antineoplastic drugs have not been established.

- It has been reported that the blood lenvatinib concentration increases in patients with severe hepatic impairment. The dose reduction should be considered for such patients, and patients should be carefully monitored with special attention to adverse events.

- The clinical study has confirmed that the maximum tolerated dose in patients with hepatocellular carcinoma who have moderate hepatic impairment (Child-Pugh score 7-8) is 8 mg once daily. These patients may be treated with the reduced dose under careful vigilance for adverse events.

7.R.5.2 Criteria for dose reduction, treatment interruption, and treatment discontinuation

The applicant's explanation about criteria for dose reduction, treatment interruption and treatment discontinuation of lenvatinib:

In Study 304 where the study criteria for dose reduction, treatment interruption and treatment discontinuation of lenvatinib were applied, the clinical usefulness of lenvatinib was demonstrated. The criteria for dose reduction, treatment interruption, and treatment discontinuation equivalent to those applied to Study 304 will be specified in the "Precautions for Dosage and Administration" section.

PMDA's view:

PMDA accepted the applicant's explanation and thus has concluded that the proposed criteria for dose reduction, treatment interruption, and treatment discontinuation should be modified as shown below and the modified statements should be included in the "Precautions for Dosage and Administration" section.

- In case of any adverse drug reaction, the treatment should be continued with the reduced dose, otherwise interrupted or discontinued depending on the symptom and severity by reference to the following criteria.

Criteria for dose reduction

	Dose reduction by 1 level	Dose reduction by 2 levels	Dose reduction by 3 levels
Body weight ≥60 kg	8 mg once daily	4 mg once daily	4 mg every other day
Body weight <60 kg	4 mg once daily	4 mg every other day	Discontinue treatment

Criteria for dose reduction, interruption, and discontinuation

Adverse drug reaction	Severity*	Measure
Hypertension	Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg	Continue lenvatinib and initiate antihypertensive drug.
	Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg despite antihypertensive treatment	Interrupt lenvatinib until the systolic blood pressure decreases to ≤150 mmHg and diastolic blood pressure to ≤95 mmHg and, initiate antihypertensive drug. If lenvatinib treatment is resumed, reduce the dose by one level.
	Grade 4 adverse drug reaction	Discontinue lenvatinib.
Haematotoxicity and proteinuria	Grade 3 adverse drug reaction (Except for clinically insignificant laboratory abnormality)	Interrupt lenvatinib until the condition resolves to the baseline level or Grade ≤2. If lenvatinib treatment is resumed, use the same dose after the first onset of the adverse drug reaction. Reduce the dose by one level following the second onset and thereafter.
	Grade 4 adverse drug reaction	Interrupt lenvatinib until the condition resolves to the baseline level or Grade ≤2. If lenvatinib treatment is resumed, reduce the dose by one level.
Other adverse drug reactions	Intolerable Grade 2 adverse drug reaction	Interrupt lenvatinib until the condition resolves to the baseline level or Grade ≤1, or continue lenvatinib at a one-level lower dose (For nausea, vomiting, diarrhoea, and thyroid function decreased, perform appropriate treatments before interruption or dose reduction of lenvatinib. If control fails, interrupt lenvatinib or reduce the dose.). If lenvatinib treatment is resumed, reduce the dose by one level.
	Grade 3 adverse drug reaction (Except for clinically insignificant laboratory abnormality)	Interrupt lenvatinib until the condition resolves to the baseline level or Grade ≤1 (For nausea, vomiting, diarrhoea, and thyroid function decreased, perform appropriate treatments before interruption of lenvatinib. If control fails, interrupt lenvatinib.). If lenvatinib treatment is resumed, reduce the dose by one level.
	Grade 4 adverse drug reaction (For non-life-threatening laboratory abnormality, take measures as done for a Grade 3 adverse drug reaction.)	Discontinue lenvatinib.

* Grade is rated in accordance with NCI-Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

7.R.6 Post-marketing investigations

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

The applicant plans to conduct a post-marketing surveillance in patients with unresectable hepatocellular carcinoma treated with lenvatinib to investigate the safety of lenvatinib in clinical use after the market launch.

The safety specification in this surveillance was planned to be hepatic encephalopathy in consideration of adverse events in Study 304.

The target sample size was 500, based on the incidence of hepatic encephalopathy in the Japanese population in Study 304.

The follow-up period was 12 months after the first dose of lenvatinib based on findings in Studies 202 and 304 that (a) most of the first episode of hepatic encephalopathy occurred within 12 months after the first dose of lenvatinib; and (b) the incidence of the concerned event 12 months after the first dose did not show any clear increasing trend.

PMDA's view:
Since the safety information of lenvatinib in Japanese patients with unresectable hepatocellular carcinoma is limited, the applicant should conduct the post-marketing surveillance to collect information about the safety of lenvatinib in patients with unresectable hepatocellular carcinoma in post-marketing clinical use in Japan and then provide the safety information obtained from the surveillance to healthcare professionals appropriately.

PMDA has concluded that the safety specification, target sample size, and follow-up period planned by the applicant are acceptable.

7.2 Adverse events observed in clinical studies

Deaths reported in clinical studies in the submitted data are described in Section "7.1 Evaluation data." Major adverse events other than deaths were as shown below.

7.2.1 Global phase I/II study (Study 202)

7.2.1.1 Phase I part

Adverse events occurred in all subjects, and adverse events for which a causal relationship to the study drug could not be ruled out also occurred in all subjects. Table 11 shows adverse events reported by ≥2 subjects in any group.

Table 11. Adverse events reported by ≥2 subjects in any group

SOC PT (MedDRA/J ver.17.0)	Number of subjects (%)							
	Arm 1*				Arm 2*			
	12 mg n = 6		16 mg n = 3		8 mg n = 6		12 mg n = 5	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	6 (100)	4 (66.7)	3 (100)	3 (100)	6 (100)	5 (83.3)	5 (100)	5 (100)
Blood and lymphatic system disorders								
Leukopenia	0	0	0	0	2 (33.3)	0	1 (20.0)	0
Neutropenia	0	0	0	0	4 (66.7)	1 (16.7)	1 (20.0)	0
Thrombocytopenia	2 (33.3)	0	1 (33.3)	0	1 (16.7)	1 (16.7)	2 (40.0)	0
Gastrointestinal disorders								
Abdominal pain	2 (33.3)	0	1 (33.3)	0	3 (50.0)	0	2 (40.0)	0
Ascites	0	0	0	0	3 (50.0)	0	3 (60.0)	0
Constipation	2 (33.3)	0	3 (100)	0	0	0	0	0
Diarrhoea	6 (100)	0	3 (100)	0	6 (100)	1 (16.7)	3 (60.0)	1 (20.0)
Epigastric discomfort	0	0	0	0	0	0	2 (40.0)	0
Nausea	2 (33.3)	0	3 (100)	0	3 (50.0)	0	4 (80.0)	0
Stomatitis	3 (50.0)	0	0	0	2 (33.3)	0	1 (20.0)	0
Vomiting	3 (50.0)	0	3 (100)	0	2 (33.3)	0	2 (40.0)	0
General disorders and administration site conditions								
Fatigue	5 (83.3)	0	3 (100)	0	5 (83.3)	0	5 (100)	1 (20.0)
General physical health deterioration	0	0	0	0	1 (16.7)	0	2 (40.0)	1 (20.0)
Oedema peripheral	0	0	2 (66.7)	0	5 (83.3)	0	1 (20.0)	0
Pyrexia	2 (33.3)	0	1 (33.3)	0	3 (50.0)	0	1 (20.0)	0
Hepatobiliary disorders								
Hyperbilirubinaemia	2 (33.3)	1 (16.7)	1 (33.3)	0	5 (83.3)	1 (16.7)	4 (80.0)	2 (40.0)
Infections and infestations								
Gingivitis	2 (33.3)	0	0	0	0	0	0	0
Investigations								
ALT increased	3 (50.0)	1 (16.7)	0	0	0	0	3 (60.0)	0
AST increased	4 (66.7)	1 (16.7)	0	0	0	0	3 (60.0)	2 (40.0)
Blood ALP increased	3 (50.0)	0	0	0	0	0	2 (40.0)	0
Blood LDH increased	3 (50.0)	0	0	0	0	0	1 (20.0)	0
Blood thyroid stimulating hormone increased	5 (83.3)	0	1 (33.3)	0	2 (33.3)	0	1 (20.0)	0
C-reactive protein increased	2 (33.3)	0	1 (33.3)	0	1 (16.7)	0	1 (20.0)	0
Tri-iodothyronine free decreased	2 (33.3)	0	1 (33.3)	0	0	0	1 (20.0)	0
γ-GTP increased	3 (50.0)	0	0	0	0	0	2 (40.0)	1 (20.0)
Weight decreased	3 (50.0)	0	1 (33.3)	0	3 (50.0)	0	2 (40.0)	0
Metabolism and nutrition disorders								
Decreased appetite	6 (100)	1 (16.7)	2 (66.7)	0	3 (50.0)	0	5 (100)	1 (20.0)
Hyperammonaemia	0	0	0	0	3 (50.0)	0	2 (40.0)	0
Hypoalbuminaemia	3 (50.0)	0	1 (33.3)	0	1 (16.7)	1 (16.7)	1 (20.0)	0
Hypocalcaemia	0	0	0	0	2 (33.3)	0	0	0
Hyponatraemia	1 (16.7)	0	2 (66.7)	2 (66.7)	1 (16.7)	1 (16.7)	1 (20.0)	1 (20.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Cancer pain	0	0	0	0	0	0	2 (40.0)	0
Nervous system disorder								
Headache	2 (33.3)	0	1 (33.3)	0	1 (16.7)	0	0	0
Psychiatric disorders								
Insomnia	1 (16.7)	0	2 (66.7)	0	0	0	1 (20.0)	0
Renal and urinary disorders								
Proteinuria	2 (33.3)	0	2 (66.7)	1 (33.3)	1 (16.7)	0	2 (40.0)	0
Respiratory, thoracic and mediastinal disorders								
Dysphonia	2 (33.3)	0	1 (33.3)	0	2 (33.3)	0	3 (60.0)	0
Epistaxis	1 (16.7)	0	1 (33.3)	0	2 (33.3)	0	0	0

SOC PT (MedDRA/J ver.17.0)	Number of subjects (%)							
	Arm 1*				Arm 2*			
	12 mg n = 6		16 mg n = 3		8 mg n = 6		12 mg n = 5	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Skin and subcutaneous tissue disorders								
Palmar-plantar erythrodysaesthesia syndrome	5 (83.3)	1 (16.7)	3 (100)	0	3 (50.0)	0	2 (40.0)	0
Rash	3 (50.0)	0	0	0	2 (33.3)	0	1 (20.0)	0
Vascular disorders								
Hypertension	5 (83.3)	4 (66.7)	3 (100)	2 (66.7)	3 (50.0)	2 (33.3)	4 (80.0)	2 (40.0)

* Arm 1 included patients with Child-Pugh liver function class A (5 or 6 points), and Arm 2 included Child-Pugh liver function class B (7 or 8 points).

Serious adverse events were reported by 2 of 6 subjects (33.3%) in the 12 mg group and 2 of 3 subjects (66.7%) in the 16 mg group in Arm 1 and by 3 of 6 subjects (50.0%) in the 8 mg group and 3 of 5 subjects (60.0%) in the 12 mg group in Arm 2. Serious adverse events reported included hyperbilirubinaemia and biliary tract infection (1 subject [16.7%] each) in the 12 mg group and pneumonia and hepatic encephalopathy (1 subject [33.3%] each) in the 16 mg group in Arm 1 as well as haematemesis, hyperbilirubinaemia, and tumour haemorrhage (1 subject [16.7%] each) in the 8 mg group and hepatic failure, tumour haemorrhage, and hepatic encephalopathy (1 subject [20.0%] each) in the 12 mg group in Arm 2. Of these, a causal relationship to the study drug could not be ruled out for biliary tract infection (1 subject) in the 12 mg group and pneumonia and hepatic encephalopathy (1 subject each) in the 16 mg group in Arm 1 as well as hyperbilirubinaemia (1 subject) in the 8 mg group and hepatic encephalopathy (1 subject) in the 12 mg group in Arm 2.

Adverse events leading to discontinuation of the study drug were reported by 1 of 3 subjects (33.3%) in the 16 mg group in Arm 1 and by 1 of 6 subjects (16.7%) in the 8 mg group and 1 of 5 subjects (20.0%) in the 12 mg group in Arm 2. Reported adverse events leading to discontinuation of the study drug included hepatic function abnormal and hepatic encephalopathy (1 subject [33.3%] each) in the 16 mg group in Arm 1 as well as ascites (1 subject [16.7%]) in the 8 mg group and hyperbilirubinaemia (1 subject [20.0%]) in the 12 mg group in Arm 2. Of these, a causal relationship to the study drug could not be ruled out for hepatic function abnormal and hepatic encephalopathy (1 subject each) in the 16 mg group in Arm 1 as well as hyperbilirubinaemia (1 subject) in the 12 mg group in Arm 2.

7.2.1.2 Phase II part

Adverse events occurred in 46 of 46 subjects (100%), and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 44 of 46 subjects (95.7%). Table 12 shows adverse events with an incidence of ≥30%.

Table 12. Adverse events with an incidence of ≥30%

SOC PT (MedDRA/J ver. 17.0)	Number of subjects (%) n = 46	
	All Grades	Grade ≥3
All adverse events	46 (100)	45 (97.8)
Blood and lymphatic system disorders		
Thrombocytopenia	16 (34.8)	10 (21.7)
Gastrointestinal disorders		
Diarrhoea	20 (43.5)	6 (13.0)
Constipation	19 (41.3)	0
Nausea	17 (37.0)	1 (2.2)
General disorders and administration site conditions		
Fatigue	25 (54.3)	0
Oedema peripheral	16 (34.8)	0
Investigations		
Weight decreased	14 (30.4)	2 (4.3)
Metabolism and nutrition disorders		
Decreased appetite	28 (60.9)	1 (2.2)
Renal and urinary disorders		
Proteinuria	28 (60.9)	9 (19.6)
Respiratory, thoracic and mediastinal disorders		
Dysphonia	17 (37.0)	0
Skin and subcutaneous tissue disorders		
Palmar-plantar erythrodysaesthesia syndrome	30 (65.2)	4 (8.7)
Rash	14 (30.4)	0
Vascular disorders		
Hypertension	35 (76.1)	25 (54.3)

Serious adverse events were reported by 22 of 46 subjects (47.8%). Reported serious adverse events included hepatic encephalopathy (5 subjects [10.9%]), renal impairment (3 subjects [6.5%]), oedema peripheral (2 subjects [4.3%]), and acute coronary syndrome, angina pectoris, cardiac tamponade, gastritis, nausea, oesophageal varices haemorrhage, vomiting, cholecystitis, cholecystitis acute, jaundice cholestatic, portal vein thrombosis, pneumonia, septic shock, hypoalbuminaemia, hypoglycaemia, cancer pain, lymphoma, tumour rupture, syncope, proteinuria, haemoptysis, and respiratory failure (1 subject [2.2%] each). Of these, a causal relationship to the study drug could not be ruled out for hepatic encephalopathy (4 subjects), renal impairment (3 subjects), oedema peripheral (2 subjects), and nausea, vomiting, respiratory failure, angina pectoris, syncope, hypoalbuminaemia, cholecystitis acute, cholecystitis, acute coronary syndrome, and proteinuria (1 subject each).

Adverse events leading to discontinuation of the study drug were reported by 16 of 46 subjects (34.8%). Reported adverse events leading to discontinuation of the study drug included proteinuria (5 subjects [10.9%]) and acute coronary syndrome, angina pectoris, ascites, oedema peripheral, jaundice cholestatic, portal vein thrombosis, pneumonia, platelet count decreased, tumour rupture, hepatic encephalopathy, renal impairment, and haemoptysis (1 subject [2.2%] each). Of these, a causal relationship to the study drug could not be ruled out for proteinuria (5 subjects) and angina pectoris, hepatic encephalopathy, ascites, oedema peripheral, acute coronary syndrome, and renal impairment (1 subject each).

7.2.2 Global phase III study (Study 304)

Adverse events occurred in 470 of 476 subjects (98.7%) in the lenvatinib group and in 472 of 475 subjects (99.4%) in the sorafenib group, and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 447 of 476 subjects (93.9%) in the lenvatinib group and in 452

of 475 subjects (95.2%) in the sorafenib group. Table 13 shows adverse events with an incidence of ≥10% in any group.

Table 13. Adverse events with an incidence of ≥10% in any group

SOC PT (MedDRA/J ver. 19.1)	Number of subjects (%)			
	Lenvatinib n = 476		Sorafenib n = 475	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	470 (98.7)	359 (75.4)	472 (99.4)	318 (66.9)
Endocrine disorders				
Hypothyroidism	80 (16.8)	0	8 (1.7)	0
Gastrointestinal disorders				
Diarrhoea	184 (38.7)	20 (4.2)	223 (46.9)	20 (4.2)
Nausea	92 (19.3)	4 (0.8)	70 (14.7)	4 (0.8)
Abdominal pain	82 (17.2)	8 (1.7)	87 (18.3)	13 (2.7)
Vomiting	79 (16.6)	6 (1.3)	36 (7.6)	5 (1.1)
Constipation	76 (16.0)	3 (0.6)	52 (10.9)	0
Ascites	69 (14.5)	18 (3.8)	45 (9.5)	14 (2.9)
Abdominal pain upper	58 (12.2)	6 (1.3)	40 (8.4)	6 (1.3)
Stomatitis	45 (9.5)	1 (0.2)	56 (11.8)	2 (0.4)
General disorders and administration site conditions				
Fatigue	142 (29.8)	18 (3.8)	119 (25.1)	17 (3.6)
Pyrexia	69 (14.5)	0	63 (13.3)	1 (0.2)
Oedema peripheral	66 (13.9)	4 (0.8)	33 (6.9)	1 (0.2)
Asthenia	54 (11.3)	14 (2.9)	48 (10.1)	11 (2.3)
Investigations				
Weight decreased	149 (31.3)	36 (7.6)	107 (22.5)	14 (2.9)
Platelet count decreased	87 (18.3)	26 (5.5)	59 (12.4)	16 (3.4)
Blood bilirubin increased	72 (15.1)	31 (6.5)	63 (13.3)	23 (4.8)
AST increased	65 (13.7)	24 (5.0)	80 (16.8)	39 (8.2)
ALT increased	53 (11.1)	16 (3.4)	51 (10.7)	16 (3.4)
Metabolism and nutrition disorders				
Decreased appetite	163 (34.2)	22 (4.6)	127 (26.7)	6 (1.3)
Musculoskeletal and connective tissue disorders				
Back pain	50 (10.5)	1 (0.2)	31 (6.5)	5 (1.1)
Renal and urinary disorders				
Proteinuria	117 (24.6)	27 (5.7)	54 (11.4)	8 (1.7)
Respiratory, thoracic and mediastinal disorders				
Dysphonia	113 (23.7)	1 (0.2)	57 (12.0)	0
Skin and subcutaneous tissue disorders				
Palmar-plantar erythrodysaesthesia syndrome	128 (26.9)	14 (2.9)	249 (52.4)	54 (11.4)
Rash	46 (9.7)	0	76 (16.0)	2 (0.4)
Alopecia	14 (2.9)	0	120 (25.3)	0
Vascular disorders				
Hypertension	199 (41.8)	111 (23.3)	145 (30.5)	68 (14.3)

Serious adverse events were reported by 207 of 476 subjects (43.5%) in the lenvatinib group and 144 of 475 subjects (30.3%) in the sorafenib group. Serious adverse events reported by ≥5 subjects in any group included hepatic encephalopathy (21 subjects [4.4%]), hepatic failure (14 subjects [2.9%]), ascites (12 subjects [2.5%]), decreased appetite, and malignant neoplasm progression (11 subjects [2.3%] each), diarrhoea (8 subjects [1.7%]), oesophageal varices haemorrhage, jaundice cholestatic, sepsis, asthenia, and blood bilirubin increased (7 subjects [1.5%] each), abdominal pain, pyrexia, upper gastrointestinal haemorrhage, and vomiting (6 subjects [1.3%] each), pneumonia, general physical health deterioration, and dyspnoea (5 subjects [1.1%] each) in the lenvatinib group; and malignant neoplasm progression (14 subjects [2.9%]), ascites (11 subjects [2.3%]), abdominal pain (10 subjects [2.1%]), hepatic failure (8 subjects [1.7%]), oesophageal varices haemorrhage, pyrexia, back pain, and pathological fracture (5

subjects [1.1%] each) in the sorafenib group. Of these, a causal relationship to the study drug could not be ruled out for hepatic encephalopathy (9 subjects), decreased appetite (8 subjects), diarrhoea (7 subjects), ascites (6 subjects), hepatic failure (5 subjects), asthenia (4 subjects), pyrexia, blood bilirubin increased, upper gastrointestinal haemorrhage, and oesophageal varices haemorrhage (3 subjects each), jaundice cholestatic and vomiting (2 subjects each), and pneumonia, dyspnoea, general physical health deterioration, and sepsis (1 subject each) in the lenvatinib group; and pyrexia (4 subjects), ascites and hepatic failure (3 subjects each), and abdominal pain (1 subject) in the sorafenib group.

Adverse events leading to discontinuation of the study drug were reported by 94 of 476 subjects (19.7%) in the lenvatinib group and by 69 of 475 subjects (14.5%) in the sorafenib group. Adverse events leading to discontinuation of the study drug reported by ≥3 subjects in any group included fatigue and hepatic encephalopathy (7 subjects [1.5%] each), blood bilirubin increased (6 subjects [1.3%]), hepatic failure (5 subjects [1.1%]), jaundice cholestatic, proteinuria, cerebral haemorrhage, myocardial infarction, and sepsis (3 subjects [0.6%] each) in the lenvatinib group; and abdominal pain and fatigue (5 subjects [1.1%] each), general physical health deterioration and ascites (4 subjects [0.8%] each), and hepatic failure, jaundice, palmar-plantar erythrodysaesthesia syndrome (3 subjects [0.6%] each) in the sorafenib group. Of these, a causal relationship to the study drug could not be ruled out for fatigue and blood bilirubin increased (4 subjects each), proteinuria, cerebral haemorrhage, and hepatic encephalopathy (3 subjects each), hepatic failure, jaundice cholestatic, and myocardial infarction (2 subjects each), and sepsis (1 subject) in the lenvatinib group; and palmar-plantar erythrodysaesthesia syndrome (3 subjects), fatigue and abdominal pain (2 subjects each), and hepatic failure and jaundice (1 subject each) in the sorafenib 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 assessment is currently ongoing. The results and PMDA’s conclusion will be reported in Review Report (2).

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

The assessment is currently ongoing. The results and PMDA’s conclusion will be reported in Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that lenvatinib has efficacy in the treatment of unresectable hepatocellular carcinoma, and that lenvatinib has acceptable safety in view of its benefits. Lenvatinib is clinically meaningful because it offers a treatment option for patients with unresectable hepatocellular carcinoma. In addition, PMDA considers it necessary to discuss the indication, dosage and administration, and post-marketing investigations, etc. further.

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

Review Report (2)

February 14, 2018

Product Submitted for Approval

Brand Name	Lenvima Capsules 4 mg
Non-proprietary Name	Lenvatinib Mesilate
Applicant	Eisai Co., Ltd
Date of Application	June 23, 2017

List of Abbreviations
See Appendix.

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

As a result of the review in Section "7.R.2 Efficacy" of the Review Report (1), PMDA has concluded that the efficacy of lenvatinib in patients with systemic chemotherapy-naive unresectable hepatocellular carcinoma was demonstrated, because the global phase III study (Study 304) showed non-inferiority of lenvatinib to sorafenib in OS, the primary endpoint.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.2 Safety

According to the review in Section "7.R.3 Safety" of the Review Report (1), PMDA has concluded that adverse events requiring caution in the treatment with lenvatinib in patients with systemic chemotherapy-naive unresectable hepatocellular carcinoma are hypertension/hypertensive crisis, infections, renal disorder, haemorrhage-related events, palmar-plantar erythrodysaesthesia syndrome, haematotoxicity, liver disorder, arrhythmia, cardiac function disturbance, hypocalcaemia, thromboembolism, gastrointestinal perforation and gastrointestinal fistulae, posterior reversible encephalopathy syndrome, wound healing delayed, and blood thyroid stimulating hormone increased. They were identified as caution-requiring adverse events of lenvatinib at its initial approval for unresectable thyroid cancer. Patients should be closely monitored for these events as practiced in the treatment for unresectable thyroid cancer.

PMDA further concluded that, although the treatment requires caution with these adverse events during treatment, lenvatinib is tolerable in patients with hepatocellular carcinoma as well, as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy by appropriate means of adverse event monitoring and control, treatment interruption, etc.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indication

As a result of the review described in Section "7.R.4 Clinical positioning and indication" of the Review Report (1), PMDA has concluded that the indication of lenvatinib should be "unresectable hepatocellular carcinoma," as proposed, with the following cautionary advice in the "Precautions for Indications" section.

Precautions for Indications

- The efficacy and safety of lenvatinib have not been established in patients with hepatocellular carcinoma for whom local therapies (percutaneous ethanol injection, radiofrequency ablation, microwave coagulation, hepatic artery embolization/TACE, radiation, etc.) are indicated.

- Eligible patients should be selected based on a thorough understanding of the efficacy and safety of lenvatinib as well as the characteristics of patients enrolled in the clinical studies, e.g., severity of hepatic impairment, described in the "Clinical Studies" section.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to define the Indication and Precautions for Indications as presented above, and the applicant accepted it.

1.4 Dosage and administration

As a result of the review described in Section "7.R.5 Dosage and administration" of the Review Report (1), PMDA has concluded that the dosage and administration of lenvatinib should be "The usual adult dosage is determined according to the body weight; 12 mg for patients weighing ≥60 kg or 8 mg for patients weighing <60 kg, administered orally once daily. The dose may be reduced according to the patient's condition." This should be presented with the following precautions for dosage and administration.

Precautions for Dosage and Administration

- The efficacy and safety of the concomitant use of lenvatinib with other antineoplastic drugs have not been established.

- It has been reported that the blood lenvatinib concentration increases in patients with severe hepatic impairment. The dose reduction should be considered for such patients, and patients should be carefully monitored with special attention to adverse events.

- The clinical study has confirmed that the maximum tolerated dose in patients with hepatocellular carcinoma who have moderate hepatic impairment (Child-Pugh score 7-8) is 8 mg once daily. These patients may be treated with the reduced dose under careful vigilance for adverse events.

- In case of any adverse drug reaction, the treatment should be continued with the reduced dose, otherwise interrupted or discontinued depending on the symptom and severity by reference to the following criteria.

Criteria for dose reduction

	Dose reduction by 1 level	Dose reduction by 2 levels	Dose reduction by 3 levels
Body weight ≥60 kg	8 mg once daily	4 mg once daily	4 mg every other day
Body weight <60 kg	4 mg once daily	4 mg every other day	Discontinue treatment

Criteria for dose reduction, interruption, and discontinuation

Adverse drug reaction	Severity*	Measure
Hypertension	Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg	Continue lenvatinib and initiate antihypertensive drug.
	Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg despite antihypertensive treatment	Interrupt lenvatinib until the systolic blood pressure decreases to ≤150 mmHg and diastolic blood pressure to ≤95 mmHg and initiate antihypertensive drug. If lenvatinib treatment is resumed, reduce the dose by one level.
	Grade 4 adverse drug reaction	Discontinue lenvatinib.
Haematotoxicity and proteinuria	Grade 3 adverse drug reaction (Except for clinically insignificant laboratory abnormality)	Interrupt lenvatinib until the condition resolves to the baseline level or Grade ≤2. If lenvatinib treatment is resumed, use the same dose after the first onset of the adverse drug reaction. Reduce the dose by one level following the second onset and thereafter.
	Grade 4 adverse drug reaction	Interrupt lenvatinib until the condition resolves to the baseline level or Grade ≤2. If lenvatinib treatment is resumed, reduce the dose by one level.
Other adverse drug reactions	Intolerable Grade 2 adverse drug reaction	Interrupt lenvatinib until the condition resolves to the baseline level or Grade ≤1, or continue lenvatinib at a one-level lower dose (For nausea, vomiting, diarrhoea, and thyroid function decreased, perform appropriate treatments before interruption or dose reduction of lenvatinib. If control fails, interrupt lenvatinib or reduce the dose). If lenvatinib treatment is resumed, reduce the dose by one level.
	Grade 3 adverse drug reaction (Except for clinically insignificant laboratory abnormality)	Interrupt lenvatinib until the condition resolves to the baseline level or Grade ≤1 (For nausea, vomiting, diarrhoea, and thyroid function decreased, perform appropriate treatments before interruption of lenvatinib. If control fails, interrupt lenvatinib.). If lenvatinib treatment is resumed, reduce the dose by one level.
	Grade 4 adverse drug reaction (For non-life-threatening laboratory abnormality, take measures as done for a Grade 3 adverse drug reaction.)	Discontinue lenvatinib.

* Grade is rated in accordance with NCI-CTCAE version 4.0.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors:

- Preferably, information about the occurrence of DLT in Arm 2 (of patients with Child-Pugh liver function class B [7-9 points], patients with class B [7 or 8 points]) in the phase I part in the global

phase I/II study (Study 202) [see Section 7.1.1.1 of the Review Report (1)] should be provided along with body weight of patients treated with lenvatinib via written materials.

- The body weight-based criteria for dose reduction should preferably be changed to ones based on the initial dose so that the criteria can also be used for patients with hepatocellular carcinoma who have moderate or severer hepatic impairment and start receiving lenvatinib at 8 mg.

PMDA's view:
In response to the comments about the criteria for dose reduction from the Expert Discussion, the criteria should be defined based on the initial dose but not body weight, and thus modified as shown below.

Criteria for dose reduction

Initial dose	Dose reduction by 1 level	Dose reduction by 2 levels	Dose reduction by 3 levels
12 mg once daily	8 mg once daily	4 mg once daily	4 mg every other day
8 mg once daily	4 mg once daily	4 mg every other day	Discontinue treatment

Based on the above, PMDA instructed the applicant to provide the following information about Arm 2 in the phase I part in Study 202 and then specify the dosage and administration and precautions for dosage and administration as described above, and the applicant accepted it.

- Median body weight (range) (kg) in the 8 mg group and 12 mg group was 65.3 (58.5, 70.4) and 62.9 (55.8, 71.3), respectively.

- DLT occurred only in the 12 mg group (2 of 5 subjects), and both subjects weighed ≥60 kg.

1.5 Risk management plan (draft)

In order to investigate the safety of lenvatinib in routine clinical use in the post-marketing setting, the applicant plans to conduct post-marketing surveillance in patients with unresectable hepatocellular carcinoma treated with lenvatinib (the target sample size, 500 subjects; follow-up period, 12 months after the first dose of lenvatinib).

PMDA's conclusions:
Based on the review in Section "7.R.6 Post-marketing investigations" of the Review Report (1), the applicant should conduct the post-marketing surveillance aiming to collect safety data of lenvatinib in routine clinical use and provide the obtained safety information to healthcare professionals appropriately. The applicant's surveillance plan, the safety specification, target sample size, and follow-up period are acceptable.

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

In view of the discussion above, PMDA has concluded that the risk management plan (draft) should include the safety specification presented in Table 14, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 15 and 16.

Table 14. Safety and efficacy specifications in the risk management plan (draft)

Safety specification*		
Important identified risks	Important potential risks	Important missing information
• Hypertension • Haemorrhage (including haemorrhage carotid artery associated with tumor regression or necrosis and tumour haemorrhage) • Arterial thromboembolism • Venous thromboembolism • Liver disorder • Renal disorder • Gastrointestinal perforation and gastrointestinal fistulae • Posterior reversible encephalopathy syndrome • Cardiac disorder • Hand and foot syndrome • Infections • Haematotoxicity • Hypocalcaemia • Wound healing delayed	• None	None
Efficacy specification		
None		

* No changes for this partial change application.

Table 15. 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 surveys in patients with unresectable thyroid cancer • <u>Post-marketing surveillance in patients with unresectable hepatocellular carcinoma</u> • Post-marketing clinical study (extension study of Study 303)	• <u>Preparation and provision of materials for healthcare professionals</u>

Underline, Activities planned for the indication to be added through this application

Table 16. Outline of post-marketing surveillance plan (draft)

Objective	To investigate the safety of lenvatinib in post-marketing routine clinical use
Survey method	Central registration system
Population	Patients with unresectable hepatocellular carcinoma
Observation period	12 months
Planned sample size	500
Main survey items	Safety specification, hepatic encephalopathy Other: patient characteristics (age, ECOG PS, Child-Pugh score, comorbidity, past history, etc.), history of treatment against the primary disease, treatment status of lenvatinib, concomitant medications and therapies, adverse events, etc.

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

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

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

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

The new drug application data (CTD 5.3.5.1.1, CTD 5.3.5.2.1, CTD 5.3.5.2.2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that the clinical studies as a whole were conducted in compliance with GCP and that there should be no obstacle to conducting its review based on the application documents submitted. Meanwhile, the following error was found in some study sites, although no significant impact on the overall evaluation of the studies. The error was communicated to the heads of the concerned study sites for correction.

Finding requiring corrective action
Study sites

- Deviations from the study protocol (non-compliance with the provisions for imaging of computerized tomography [CT] or magnetic resonance imaging [MRI])

3. 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 shown below, with the following condition of approval. The proper use of the product, however, should be premised on the appropriate provision of cautionary advice in the package insert and any other relevant information in the post-marketing setting. The product should be used under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy and at medical institutions capable of emergency response. This application is intended to add a non-orphan indication to the approved orphan drug with a new active ingredient, the appropriate re-examination period for the indication in this application should be 5 years and 10 months.

Indication (Underline denotes addition.)
Unresectable thyroid cancer, unresectable hepatocellular carcinoma

Dosage and Administration (Underline denotes addition.)
Unresectable thyroid cancer
The usual adult dosage is 24 mg of lenvatinib administered orally once daily. The dose may be reduced according to the patient's condition.

Unresectable hepatocellular carcinoma
The usual adult dosage is determined according to the body weight; 12 mg for patients weighing ≥60 kg or 8 mg for patients weighing <60 kg, administered orally once daily. The dose may be reduced according to the patient's condition.

Condition of Approval
The applicant is required to develop and appropriately implement a risk management plan.

Warnings (No change)

Lenvatinib should be administered only to patients who are considered eligible for the treatment at medical institutions well equipped to cope with emergencies under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy. Consent should be obtained, before the initiation of treatment, from the patient or his/her family member who has been provided with a thorough explanation of the benefits and risks of the therapy.

Contraindications (No change)

1. Patients with a history of hypersensitivity to any ingredient in lenvatinib
2. Pregnant women or women who may be pregnant

Precautions for Indications (Underline denotes addition.)

Unresectable thyroid cancer

1. The efficacy and safety of lenvatinib in radioiodine-naïve patients with differentiated thyroid cancer have not been established.

2. Eligible patients should be selected based on a thorough understanding of the efficacy and safety of lenvatinib and the histopathological type etc., of the patients enrolled in the clinical studies described in the "Clinical Studies" section.

Unresectable hepatocellular carcinoma

1. The efficacy and safety of lenvatinib have not been established in patients with hepatocellular carcinoma for whom local therapies (percutaneous ethanol injection, radiofrequency ablation, microwave coagulation, hepatic artery embolization/transcatheter arterial chemoembolization, radiation, etc.) are indicated.

2. Eligible patients should be selected based on a thorough understanding of the efficacy and safety of lenvatinib as well as the characteristics of patients enrolled in the clinical studies, e.g., severity of hepatic impairment, described in the "Clinical Studies" section.

Precautions for Dosage and Administration (Underline denotes addition.)

1. The efficacy and safety of concomitant use of lenvatinib with the other antineoplastic drugs have not been established.

2. It has been reported that the blood lenvatinib concentration increases in patients with severe hepatic impairment. The dose reduction should be considered for such patients, and patients should be carefully monitored with special attention to adverse event development.

Unresectable thyroid cancer

If any adverse drug reaction is observed, lenvatinib dose should be reduced, interrupted, or discontinued, according to the symptom and severity, taking the following criteria into account. If treatment is continued at a reduced dose, the dose should be reduced to 20 mg, 14 mg, 10 mg, 8 mg, or 4 mg once daily.

Criteria for ~~interruption~~ dose reduction, ~~dose reduction~~ interruption, and discontinuation

Adverse drug reaction	Severity*	Measure
Hypertension	Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg	Continue lenvatinib, and initiate antihypertensive drug.
	Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg despite antihypertensive treatment	Interrupt lenvatinib until the systolic blood pressure decreases to ≤150 mmHg and diastolic blood pressure to ≤95 mmHg and initiate antihypertensive drug. If lenvatinib treatment is resumed, reduce the dose one-level lower.
	Grade 4 adverse drug reaction	Discontinue lenvatinib.
Other adverse drug reactions	Intolerable Grade 2 or Grade 3 adverse drug reaction	Interrupt lenvatinib until the condition resolves to the baseline or Grade ≤1. (For nausea, vomiting, and diarrhoea, perform appropriate treatments before interruption of lenvatinib. If control fails, interrupt lenvatinib.) If lenvatinib treatment is resumed, reduce the dose one-level lower.
	Grade 4 adverse drug reaction (For non-life-threatening laboratory abnormality, take measures as done for a Grade 3 adverse drug reaction.)	Discontinue lenvatinib.

* Grade is rated in accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Unresectable hepatocellular carcinoma

1. The clinical study has confirmed that the maximum tolerated dose in patients with hepatocellular carcinoma who have moderate hepatic impairment (Child-Pugh score 7-8) is 8 mg once daily. These patients may be treated with the reduced dose under careful vigilance for adverse events.

2. In case of any adverse drug reaction, the treatment should be continued with the reduced dose, otherwise interrupted or discontinued depending on the symptom and severity by reference to the following criteria.

Criteria for dose reduction

Initial dose	Dose reduction by 1 level	Dose reduction by 2 levels	Dose reduction by 3 levels
12 mg once daily	8 mg once daily	4 mg once daily	4 mg every other day
8 mg once daily	4 mg once daily	4 mg every other day	Discontinue treatment

Criteria for dose reduction, interruption, and discontinuation

Adverse drug reaction	Severity*	Measure
Hypertension	Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg	Continue lenvatinib and initiate antihypertensive drug.
	Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg despite antihypertensive treatment	Interrupt lenvatinib until the systolic blood pressure decreases to ≤150 mmHg and diastolic blood pressure to ≤95 mmHg and initiate antihypertensive drug. If lenvatinib treatment is resumed, reduce the dose by one level.
	Grade 4 adverse drug reaction	Discontinue lenvatinib.
Haematotoxicity and proteinuria	Grade 3 adverse drug reaction (Except for clinically insignificant laboratory abnormality)	Interrupt lenvatinib until the condition resolves to the baseline level or Grade ≤2. If lenvatinib treatment is resumed, use the same dose after the first onset of the adverse drug reaction. Reduce the dose by one level following the second onset and thereafter.
	Grade 4 adverse drug reaction	Interrupt lenvatinib until the condition resolves to the baseline level or Grade ≤2. If lenvatinib treatment is resumed, reduce the dose by one level.
Other adverse drug reactions	Intolerable Grade 2 adverse drug reaction	Interrupt lenvatinib until the condition resolves to the baseline level or Grade ≤1, or continue lenvatinib at a one-level lower dose (For nausea, vomiting, diarrhoea, and thyroid function decreased, perform appropriate treatments before interruption or dose reduction of lenvatinib. If control fails, interrupt lenvatinib or reduce the dose). If lenvatinib treatment is resumed, reduce the dose by one level.
	Grade 3 adverse drug reaction (Except for clinically insignificant laboratory abnormality)	Interrupt lenvatinib until the condition resolves to the baseline level or Grade ≤1 (For nausea, vomiting, diarrhoea, and thyroid function decreased, perform appropriate treatments before interruption of lenvatinib. If control fails, interrupt lenvatinib.). If lenvatinib treatment is resumed, reduce the dose by one level.
	Grade 4 adverse drug reaction (For non-life-threatening laboratory abnormality, take measures as done for a Grade 3 adverse drug reaction.)	Discontinue lenvatinib.

* Grade is rated in accordance with CTCAE version 4.0.

Appendix

List of Abbreviations

ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BID	bis in die
CI	confidence interval
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose limiting toxicity
DMSO	dimethyl sulfoxide
ECOG	Eastern Cooperative Oncology Group
ERK	extracellular signal-regulated kinase
FAS	full analysis set
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FRS2	fibroblast growth factor receptor substrate 2
HUVEC	human umbilical vein endothelial cell
IDMC	independent data monitoring committee
ITT	intention-to-treat
JSH HCC Guidelines	Clinical Practice Guidelines for Hepatocellular Carcinoma 201, edited by the Japan Society of Hepatology (2017)
KIT	stem cell factor receptor
LDH	lactate dehydrogenase
Lenvatinib	lenvatinib mesilate
MedDRA	Medical Dictionary for Regulatory Activities Japanese version
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Hepatobiliary Cancers
NCI	National Cancer Institute
OS	overall survival
Partial change application	Application for partial change approval
PDGFR	platelet-derived growth factor receptor
PDQ	Physician Data Query
PFS	progression-free survival
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PS	performance status
PT	preferred term
QD	quaque die
RET	rearranged during transfection
ROC	receiver operating characteristics
SOC	system organ class
Sorafenib	sorafenib tosilate
Study 202	Study E7080-J081-202
Study 303	Study E7080-G000-303
Study 304	Study E7080-G000-304
S6	ribosomal protein S6

S6K	ribosomal protein S6 kinase
TACE	transcatheter arterial chemoembolization
TTP	time to progression
VEGFR	vascular endothelial growth factor receptor
γ-GTP	γ-glutamyl transferase