Report on the Deliberation Results

March 3, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Lenvima Capsules 4 mg
	Lenvima Capsules 10 mg
Non-proprietary Name	Lenvatinib Mesilate (JAN*)
Applicant	Eisai Co., Ltd.
Date of Application	July 30, 2020

Results of Deliberation

In its meeting held on February 22, 2021, 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 10 years.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Review Report

February 1, 2021
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	(1) Lenvima Capsules 4 mg (2) Lenvima Capsules 10 mg
Non-proprietary Name	Lenvatinib Mesilate
Applicant	Eisai Co., Ltd.
Date of Application	July 30, 2020
Dosage Form/Strength	Each capsule contains 4.90 mg of Lenvatinib Mesilate (4 mg of lenvatinib) or 12.25 mg of Lenvatinib Mesilate (10 mg of lenvatinib).
Application Classification	Prescription drug (4) Drug with a new indication
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 469 of 2020 [*R2 yaku*], PSEHB/PED Notification No. 0605-1 dated June 5, 2020, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has a certain degree of efficacy in the treatment of unresectable thymic 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. Decreased thyroid function should be further investigated through the post-marketing surveillance.

Indications

(1) Unresectable thyroid cancer, unresectable hepatocellular carcinoma, unresectable thymic carcinoma

(2) Unresectable thyroid cancer, unresectable thymic carcinoma

(Underline denotes additions.)

Dosage and administration

(1) Unresectable thyroid cancer, unresectable thymic carcinoma

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.

(2) Unresectable thyroid cancer, unresectable thymic carcinoma

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

(Underline denotes additions.)

Approval condition

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

Attachment

Review Report (1)

December 23, 2020

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 (PMDA).

Product submitted for Approval

Brand Name	(1) Lenvima Capsules 4 mg (2) Lenvima Capsules 10 mg
Non-proprietary Name	Lenvatinib Mesilate
Applicant	Eisai Co., Ltd.
Date of Application	July 30, 2020
Dosage Form/Strength	Each capsule contains 4.90 mg of Lenvatinib Mesilate (4 mg of lenvatinib) or 12.25 mg of Lenvatinib Mesilate (10 mg of lenvatinib)
Proposed Indications	(1) Unresectable thyroid cancer, unresectable hepatocellular carcinoma, unresectable thymic carcinoma (2) Unresectable thyroid cancer, unresectable thymic carcinoma (Underline denotes additions.)

Proposed Dosage and Administration

(1) Unresectable thyroid cancer, unresectable thymic carcinoma

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.

(2) Unresectable thyroid cancer, unresectable thymic carcinoma

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

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

Lenvatinib Mesilate (hereinafter referred to as lenvatinib), discovered by the applicant, is a low molecular compound that inhibits the activity of kinases including vascular endothelial growth factor receptor (VEGFR)1, VEGFR2, VEGFR3, rearranged during transfection (RET), fibroblast growth factor receptor (FGFR)1, FGFR2, FGFR3, FGFR4, platelet-derived growth factor receptor (PDGFR) α, and KIT (a stem cell growth factor receptor). Lenvatinib is expected to inhibit the signal transduction pathway mediated by these tyrosine kinase, thereby suppressing tumor growth.

In Japan, lenvatinib was approved in March 2015 for the treatment of unresectable thyroid cancer, and in March 2018 for an additional indication, unresectable hepatocellular carcinoma.

1.2 Development history, etc.

In April 2017, for clinical development of lenvatinib for unresectable thymic carcinoma, an investigator-initiated phase II study (REMORA study) began in Japan at study centers including the National Cancer Center Hospital in patients with unresectable thymic carcinoma previously treated with platinum-based chemotherapy regimens, supported by the Project Promoting Clinical Trials for Development of New Drugs from the Japan Agency for Medical Research and Development.

As of November 2020, lenvatinib has not been approved for the indication of thymic carcinoma in any country or region.

Based mainly on the results of the REMORA study, the present partial change application was filed to add the new indication of unresectable thymic carcinoma.

Lenvatinib was designated as an orphan drug (Orphan Drug Designation No. 469 of 2020 [*R2 yaku*]) for the intended indication of “unresectable thymic carcinoma” in June 2020.

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

Since the present application is for a new indication, no quality-related data were submitted.

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

3.1 Primary pharmacodynamics

3.1.1 Antiproliferative activity against malignant tumor-derived cell lines

3.1.1.1 *In vivo* (CTD 4.2.1.1)

The antitumor effect of lenvatinib was studied in nude mice (n = 8/group) that had been subcutaneously xenografted with the human thymic carcinoma derived Ty-82 cell lines. Starting from 8 days post-xenograft (Day 1), lenvatinib was administered to the mice at 10, 30, or 100 mg/kg QD orally for 28 days, and tumor volume was calculated on Day 29. As shown in Figure 1, the antitumor effect was statistically significant in all lenvatinib groups as compared with the control group (3 mmol/L hydrochloric acid [HCl]).

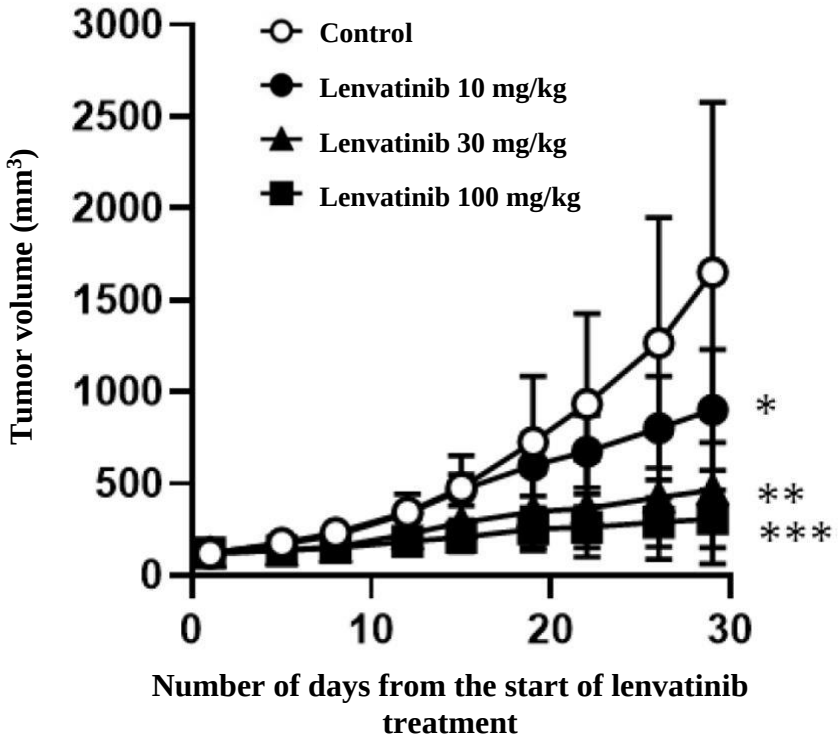

Figure 1. Antitumor effect of lenvatinib in nude mice subcutaneously xenografted with Ty-82 cell lines
n = 8; mean ± standard deviation; * $P < 0.05$ versus the control group; ** $P < 0.001$ versus the control group; *** $P < 0.0001$ versus the control group (all tested by Dunnett's mutiple comparison)

3.R Outline of the review conducted by PMDA

Based on the submitted data and discussions in the following subsections, PMDA concluded that the applicant's explanation about the non-clinical pharmacology of lenvatinib is acceptable.

3.R.1 Efficacy of lenvatinib in the treatment of thymic carcinoma

The applicant's explanation about the efficacy of lenvatinib in the treatment of thymic carcinoma:

The following observations indicate that lenvatinib has promising efficacy in the treatment of thymic carcinoma.

- Lenvatinib inhibits signal transduction mediated by VEGFR2 kinase activity, thereby suppressing angiogenesis in tumor tissue (see Review Report of Lenvima Capsules 4 mg and 10 mg, dated January 9, 2015)
- Lenvatinib showed an antitumor effect in nude mice subcutaneously xenografted with the human thymic carcinoma cell lines [see Section 3.1.1.1].

PMDA's view:

The applicant's explanation is generally acceptable. However, it remains unclear to what extent each kinase inhibited by lenvatinib is involved in tumor growth, which can be useful information for identifying eligible patients for lenvatinib treatment. Therefore, the applicant should continue to collect information, and new findings should be communicated to healthcare professionals in an appropriate manner.

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

The present application is for a new indication, and non-clinical pharmacokinetic data have already been evaluated at the initial approval. Therefore, no new data were submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

Because the present application is intended for a new indication, no data relating to toxicity testing were submitted.

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

The present application is intended for a new indication. Data relating to biopharmaceutic studies and associated analytical methods as well as clinical pharmacology data have already been evaluated for the initial approval, and no new data were submitted.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from a Japanese phase II study (Table 1).

Table 1. A clinical study on efficacy and safety

Data category	Location	Study ID	Phase	Study population	Number of subjects enrolled	Summary of dosage regimen	Main endpoints
Evaluation	Japan	REMORA	II	Patients with unresectable thymic carcinoma previously treated with platinum-based chemotherapy regimens	42	Oral lenvatinib 24 mg QD	Efficacy Safety

The following subsections outline the clinical studies. Main adverse events other than deaths that occurred in the clinical study are summarized in Section "7.2 Adverse events, etc. observed in the clinical study."

7.1 Evaluation data

7.1.1 Japanese study

7.1.1.1 Japanese phase II study (CTD 5.3.5.2-1, REMORA study [ongoing since April 2017, efficacy data cut-off on February 22, 2019; safety data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted at 8 study centers in Japan to assess the efficacy and safety of lenvatinib in patients with unresectable thymic carcinoma[1)] previously treated with platinum-based chemotherapy regimens[2)] (target sample size, 42 subjects).

Subjects received lenvatinib 24 mg orally QD. The treatment was continued until disease progression or the treatment discontinuation criteria were met.

1) Eligible patients had (1) unresectable Masaoka-Koga stage IIIa or IIIb thymic carcinoma; (2) Masaoka-Koga stage IVa or IVb thymic carcinoma; or (3) postoperative recurrent thymic carcinoma.
2) ≥1 prior platinum-based chemotherapy regimen, or prior chemoradiotherapy.

All 42 subjects enrolled in this study received lenvatinib and were included in the efficacy and safety analyses.

The primary endpoint was the response rate centrally reviewed according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1. The study was designed with 2 stages and a response rate threshold of 10%.[3)] In the first stage, the results up to 20 subjects were analyzed, and enrollment was continued when ≥1 subject was found to have responded. In the second stage involving additional subjects of 22 (a total of up to 42 subjects), the treatment was determined as effective when 8 of these subjects responded to it. The primary analysis of the study was performed when all subjects in the efficacy analysis set had undergone a follow-up period of ≥12 months.

Table 2 shows the response rate centrally reviewed according to RECIST ver.1.1, the primary endpoint of the study. The lower limit of 90% confidence interval [CI] was higher than the prespecified response rate threshold (10%) on the data cut-off date of February 22, 2019.

Table 2. Best overall response and response rate
(RECIST ver.1.1, efficacy analysis set, centrally reviewed, data cut-off on February 22, 2019)

Best overall response	n (%)
	N = 42
CR	0
PR	16 (38.1)
SD	24 (57.1)
PD	2 (4.8)
Response rate (CR + PR) (Response rate [90% CI*], %)	16 (38.1% [25.6, 52.0])

* Clopper-Pearson method

There were no deaths during treatment or within 30 days after the last dose of lenvatinib.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

Based on the following discussions, PMDA concluded that lenvatinib has a certain level of efficacy in the treatment of patients with unresectable thymic carcinoma previously treated with platinum-based chemotherapy regimens.

7.R.1.1 Efficacy endpoint and evaluation results

The applicant's explanation about the primary endpoint and the efficacy of lenvatinib in the treatment of patients with unresectable thymic carcinoma previously treated with platinum-based chemotherapy regimens in the REMORA study:

Articles report that patients with unresectable thymic carcinoma who had responded to lenvatinib were likely to show improved clinical symptoms such as chest pain and dyspnoea with reduced tumor size (*J Thorac Oncol.* 2016;11:e125-6, etc). Responding to lenvatinib is therefore considered clinically significant in this patient population, and therefore, the response rate was defined as the primary endpoint of the REMORA study.

3) The response rate threshold of 10% was specified based on the response rate of 10% to 14% reported in clinical studies (e.g., *Lung Cancer.* 2015;87:34-8) in Japan and overseas which assessed the efficacy and safety of cytotoxic antineoplastic drugs in patients with unresectable thymic carcinoma who had been previously treated with chemotherapy regimens.

In the REMORA study, the response rate [90% CI] was 38.1% [25.6, 52.0], with the lower limit of 90% CI, 25.6%, exceeding the prespecified response rate threshold of 10% [see Section 7.1.1.1]. In addition, no standard therapy has demonstrated prolonged overall survival (OS) in the patient population of the study. Given these, lenvatinib is expected to have efficacy in patients with unresectable thymic carcinoma previously treated with platinum-based chemotherapy regimens.

Figure 2 shows the best percent change from baseline in the sum of target lesion sizes centrally reviewed according to RECIST ver.1.1 in the REMORA study. The median duration of response[4] [95% CI] was 11.6 months [5.8, 18.0].[5]

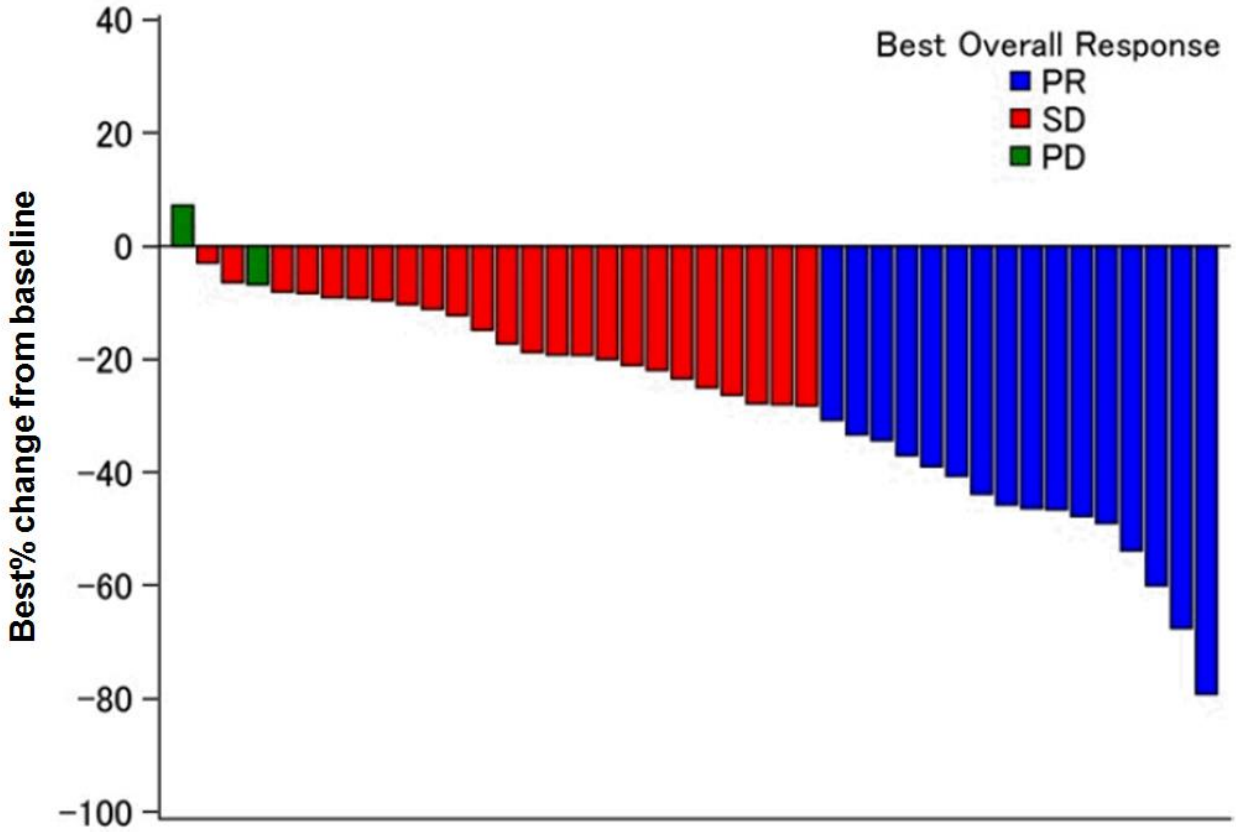

Figure 2. Best percent change from baseline in the sum of target lesion diameters (RECIST ver.1.1, efficacy analysis set, centrally reviewed)

PMDA's view:

The relationship remains unclear between the response rate and OS, the true endpoint, in patients with unresectable thymic carcinoma previously treated with platinum-based chemotherapy regimens. Therefore, the effect of lenvatinib on life extension in this patient population is difficult to evaluate based on the response

[4] The duration of response in patients achieving confirmed complete response (CR) or partial response (PR) was defined as time from the initial response (complete response [CR] or partial response [PR]) to progressive disease (PD) or death. Patients who survived or did not experience PD, or those who had started subsequent therapy were censored at the time point of the last visit or last image evaluation.

[5] The duration of response ranged from 1.9 to 21.1 months.

rate, the primary endpoint of the REMORA study. Nevertheless, the applicant's explanation about the efficacy of lenvatinib is reasonable, and the response rates and other data from the REMORA study indicated a certain level of efficacy of lenvatinib in the treatment of patients with unresectable thymic carcinoma previously treated with platinum-based chemotherapy regimens.

7.R.2 Safety [for adverse events, see Section "7.2 Adverse events, etc. observed in the clinical study"]

PMDA considers that, based on the discussions in the following subsections, the use of lenvatinib in patients with unresectable thymic carcinoma previously treated with platinum-based chemotherapy regimens requires particular caution against decreased thyroid function in addition to the adverse events[6)] that had been identified during the approval process of lenvatinib for the previously approved indications; and thus patients should be monitored closely for these adverse events during lenvatinib treatment.

Although the use of lenvatinib requires particular caution against the above-mentioned adverse events, PMDA concluded that patients with thymic carcinoma will be tolerant to lenvatinib as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy appropriately through adverse event monitoring and control and dose interruption or reduction.

7.R.2.1 Safety profile of lenvatinib

The applicant's explanation about the safety profiles of lenvatinib based on the safety data from the REMORA study:

Table 3 summarizes the safety data from the REMORA study.

Table 3. Summary of safety data (REMORA study, safety analysis set)

	n (%) N = 42
All adverse events	42 (100)
Grade ≥3 adverse events	37 (88.1)
Adverse events resulting in death	0
Serious adverse events	12 (28.6)
Adverse events leading to treatment discontinuation	4 (9.5)
Adverse events leading to dose interruption	13 (31.0)
Adverse events leading to dose reduction	42 (100)

In the REMORA study, adverse events of any grade with an incidence of ≥20% were hypertension (37 subjects, 88.1%); proteinuria (30 subjects, 71.4%); palmar-plantar erythrodysaesthesia syndrome (29 subjects, 69.0%); hypothyroidism (27 subjects, 64.3%); diarrhoea (24 subjects, 57.1%); platelet count decreased (23 subjects, 54.8%); decreased appetite (18 subjects, 42.9%); weight decreased and dysphonia (17 subjects each, 40.5%); aspartate aminotransferase (AST) increased, malaise, and stomatitis (14 subjects each, 33.3%); alanine aminotransferase (ALT) increased, nausea, headache, and fatigue (12 subjects each, 28.6%);

6) Hypertension/hypertensive crisis, infections, renal disorder, haemorrhage-related events, palmar-plantar erythrodysaesthesia syndrome, haematotoxicity, liver disorder, acute cholecystitis, arrhythmia, cardiac function disturbance, hypocalcaemia, thromboembolism, gastrointestinal perforation, gastrointestinal fistulae, pneumothorax, posterior reversible encephalopathy syndrome, delayed wound healing, interstitial lung disease, and blood thyroid stimulating hormone increased (see "Review Report of Lenvima Capsules 4 mg and 10 mg dated January 9, 2015," "Review Report of Lenvima Capsules 4 mg dated February 14, 2018," etc.)

hypoalbuminaemia (11 subjects, 26.2%), and vomiting (10 subjects, 23.8%). Grade ≥3 adverse events with an incidence of ≥5% were hypertension (27 subjects, 64.3%); diarrhoea (4 subjects, 9.5%); weight decreased and palmar-plantar erythrodysaesthesia syndrome (3 subjects each, 7.1%). An adverse event leading to dose interruption with an incidence of ≥5% was diarrhoea (3 subjects, 7.1%), and adverse events leading to dose reduction with an incidence of ≥5% were proteinuria (18 subjects, 42.9%); palmar-plantar erythrodysaesthesia syndrome (11 subjects, 26.2%); hypertension (10 subjects, 23.8%); decreased appetite and malaise (6 subjects each, 14.3%); diarrhoea and protein urine (5 subjects each, 11.9%); arthralgia and fatigue (3 subjects each, 7.1%). There were no serious adverse events or adverse events leading to treatment discontinuation with an incidence of ≥5%.

The applicant's explanation about the differences in the safety profiles of lenvatinib between patients with unresectable thymic carcinoma in the REMORA study and patients with unresectable thyroid cancer in Study 303,[7)] in which lenvatinib was evaluated for the approved indication using the dosage regimen identical to that of the REMORA study:

Table 4 summarizes the safety data from the REMORA study and the lenvatinib group in Study 303.

Table 4. Summary of safety data from REMORA study and Study 303

	n (%)	
	Thymic carcinoma (REMORA)	Thyroid cancer (Study 303)
	N = 42	N = 261
All adverse events	42 (100)	260 (99.6)
Grade ≥3 adverse events	37 (88.1)	227 (87.0)
Adverse events resulting in death	0	20 (7.7)
Serious adverse events	12 (28.6)	139 (53.3)
Adverse events leading to treatment discontinuation	4 (9.5)	46 (17.6)
Adverse events leading to dose interruption	13 (31.0)	217 (83.1)
Adverse events leading to dose reduction	42 (100)	178 (68.2)

Adverse events of any grade with a ≥20% higher incidence in the REMORA study than in Study 303 were proteinuria (30 subjects [71.4%] in the REMORA study, 88 subjects [33.7%] in Study 303), palmar-plantar erythrodysaesthesia syndrome (29 subjects [69.0%], 84 subjects [32.2%]), hypothyroidism (27 subjects [64.3%], 14 subjects [5.4%]), platelet count decreased (23 subjects [54.8%], 17 subjects [6.5%]), malaise (14 subjects [33.3%], 14 subjects [5.4%]), AST increased (14 subjects [33.3%], 18 subjects [6.9%]), and ALT increased (12 subjects [28.6%], 20 subjects [7.7%]). A Grade ≥3 adverse event with a ≥5% higher incidence in the REMORA study than in Study 303 was hypertension (27 subjects [64.3%], 112 subjects [42.9%]). Adverse events leading to dose reduction with a ≥5% higher incidence in the REMORA study than in Study 303 were proteinuria (18 subjects [42.9%], 28 subjects [10.7%]), palmar-plantar erythrodysaesthesia syndrome (11 subjects [26.2%], 20 subjects [7.7%]), hypertension (10 subjects [23.8%], 35 subjects [13.4%]), malaise (6 subjects [14.3%], 2 subjects [0.8%]), and protein urine (5 subjects [11.9%], 0). There were no adverse events

7) Study 303 is a global phase III study in patients with locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer.

resulting in death, serious adverse events, or adverse events leading to treatment discontinuation or dose interruption with a ≥5% higher incidence in the REMORA study than in Study 303.

PMDA's view:
In the REMORA study, some adverse events occurred at a higher incidence than that in patients with thyroid cancer, for which lenvatinib has already been approved. However, most of these adverse events are known, and there were no trends towards increasing incidence of adverse events resulting in death or serious adverse events. Given this, etc., patients with thymic carcinoma will be tolerant to lenvatinib as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy appropriately through adverse event monitoring and control and dose interruption or reduction.

In the following subsections, PMDA reviews adverse events primarily focusing on decreased thyroid function, which incidence was particularly high in patients with thymic carcinoma as compared with that in patients with thyroid cancer.

7.R.2.2 Decreased thyroid function

The applicant's explanation about decreased thyroid function associated with lenvatinib:
Events classified under Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) of "hypothyroidism," "blood thyroid stimulating hormone increased," "thyroxine decreased," "tri-iodothyronine decreased," "thyroxine free decreased," "tri-iodothyronine free decreased," "thyroglobulin decreased," and "thyroid hormones decreased" were counted.

Table 5 shows the incidence of decreased thyroid function in the REMORA study.

Table 5. Incidence of decreased thyroid function (REMORA study)

PT (MedDRA/J ver.19.1)	n (%) N = 42	
	All Grades	Grade ≥3
Decreased thyroid function*	31 (73.8)	0
Hypothyroidism	27 (64.3)	0
Blood thyroid stimulating hormone increased	6 (14.3)	0

* Total of events subject to analysis

In the REMORA study, there were no decreased thyroid function-related events resulting in death, serious, or leading to treatment discontinuation, dose interruption, or dose reduction.

In the REMORA study, the median time to the initial onset of decreased thyroid function events was 29 days (range, 8-168).

Table 6 shows detailed data of patients who developed serious decreased thyroid function after lenvatinib treatment (causally related with lenvatinib) reported in post-marketing experience in Japan. In the clinical studies[8)] of lenvatinib conducted in Japan and overseas, no serious decreased thyroid function were reported.

Table 6. List of patients who developed serious decreased thyroid function (a causal relationship with lenvatinib exists) in the post-marketing setting in Japan

Age	Sex	Primary disease	Dose (mg)	PT (MedDRA/J ver.23.0)	Grade	Time to onset (days)	Duration (days)	Action taken with lenvatinib treatment	Outcome
6[redacted]	F	Thyroid cancer	24	Hypothyroidism	2	29	77	Dose reduction	Resolving
8[redacted]	F	Hepatocellular carcinoma	Unknown	Hypothyroidism	Unknown	24	Unknown	Discontinued	Resolving
50s	M	Hepatocellular carcinoma	12	Hypothyroidism	Unknown	20	96	Discontinued	Resolved
8[redacted]	F	Hepatocellular carcinoma	8	Hypothyroidism	Unknown	11	2	Discontinued	Resolved
7[redacted]	M	Hepatocellular carcinoma	8	Hypothyroidism	Unknown	20	22	Dose reduction	Resolved
6[redacted]	M	Hepatocellular carcinoma	12	Hypothyroidism	Unknown	36	Unknown	Discontinued	Not resolved
7[redacted]	M	Hepatocellular carcinoma	8	Hypothyroidism	Unknown	16	42	Discontinued	Resolved
8[redacted]	F	Hepatocellular carcinoma	8	Hypothyroidism	3	14	29	Dose reduction	Resolved
7[redacted]	M	Hepatocellular carcinoma	8	Hypothyroidism	Unknown	57	Unknown	Dose reduction	Unknown
7[redacted]	M	Hepatocellular carcinoma	12	Hypothyroidism	Unknown	53	5	Discontinued	Resolved
8[redacted]	M	Hepatocellular carcinoma	8	Hypothyroidism	2	32	30	Dose reduction	Resolved
7[redacted]	M	Hepatocellular carcinoma	12	Hypothyroidism	3	71	71	Discontinued	Resolved
7[redacted]	M	Hepatocellular carcinoma	12	Hypothyroidism	Unknown	8	Unknown	Discontinued	Not resolved
6[redacted]	M	Hepatocellular carcinoma	8	Hypothyroidism	Unknown	28	31	Discontinued	Resolving
6[redacted]	F	Hepatocellular carcinoma	8	Hypothyroidism	3	40	44	Dose interruption	Resolved
70s	M	Hepatocellular carcinoma	8	Hypothyroidism	Unknown	Unknown	Unknown	Dose reduction	Resolved
7[redacted]	M	Hepatocellular carcinoma	8	Hypothyroidism	2	8	15	Dose reduction	Resolving
8[redacted]	F	Hepatocellular carcinoma	8	Hypothyroidism	Unknown	24	29	Discontinued	Resolved
7[redacted]	M	Hepatocellular carcinoma	8	Hypothyroidism	3	1	Unknown	Discontinued	Not resolved

PMDA asked the applicant to explain how decreased thyroid function develops in association with lenvatinib treatment and its risk factors.

The applicant's response:

8) REMORA study, Study 303, Study 304 (a global phase III study in patients with systemic chemotherapy-naïve unresectable hepatocellular carcinoma), Study 201 (a foreign phase II study in patients with radioactive iodine-refractory differentiated thyroid cancer or medullary thyroid cancer), Study 202 (a global phase I/II study in patients with unresectable hepatocellular carcinoma for which no standard therapy exists), and Study 208 (a Japanese phase II study in patients with locally-advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer, medullary thyroid cancer, or anaplastic thyroid carcinoma.

Lenvatinib and other VEGFR inhibitors may act on the parenchyma and blood vessels in the thyroid gland, possibly causing tissue damage and ischemia of thyroid tissue (*Ann Intern Med.* 2006;145:660-4, *Am J Physiol Heart Circ Physiol.* 2006;290:H560-76). However, the mechanism of decreased thyroid function caused by lenvatinib and its risk factors remain undetermined.

PMDA's view:
In the REMORA study, decreased thyroid function occurred in a certain percentage of subjects receiving lenvatinib, and serious decreased thyroid function for which a causal relationship to lenvatinib could not be ruled out were reported in post-marketing experience in Japan. Given this situation, patients should be closely monitored for decreased thyroid function while treated with using lenvatinib. Therefore, information about decreased thyroid function that occurred in the REMORA study should be provided to healthcare professionals in an appropriate manner via the package insert, etc. Furthermore, the occurrence of decreased thyroid function should be carefully monitored in the post-marketing setting, and new findings should be communicated to healthcare professionals in an appropriate manner.

7.R.3 Clinical positioning and indications

Initially, the proposed indication of lenvatinib was "unresectable thymic carcinoma." The "Precautions Concerning Indications" section mentioned that the efficacy and safety of lenvatinib have not been established in patients with chemotherapy-naïve thymic carcinoma or in its combination use with radiotherapy. However, after the submission of the application for partial change, the applicant explained that the "Precautions Concerning Indications" section would be modified as follows, and the cautionary statement about the combination use with radiotherapy would be presented in the "Precautions Concerning Dosage and Administration" section [see Section 7.R.4].

- The efficacy and safety of lenvatinib in patients with chemotherapy-naïve thymic carcinoma have not been established.
- The efficacy and safety of lenvatinib as neoadjuvant or adjuvant chemotherapy have not been established.

Based on the discussions in the following subsections as well as those in Sections "7.R.1 Efficacy" and "7.R.2 Safety," PMDA concluded that it is appropriate to define the indication of lenvatinib as "unresectable thymic carcinoma" as proposed by the applicant, with the following cautionary statements provided in the "Precautions Concerning Indications" section:

- The efficacy and safety of lenvatinib as neoadjuvant chemotherapy have not been established.
- Eligible patients should be selected based on a thorough understanding of the efficacy and safety of lenvatinib as well as the information described in the "Clinical Studies" section.

7.R.3.1 Clinical positioning and indication of lenvatinib

In the clinical practice guidelines and major textbooks of clinical oncology published in Japan and other countries, the following description on lenvatinib in patients with unresectable thymic carcinoma was found:
Clinical practice guidelines

- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (v.1.2021):

Lenvatinib is recommended as a treatment option for patients with unresectable thymic carcinoma previously treated with chemotherapy.

The applicant's explanation about the clinical positioning and indication of lenvatinib:
Based on the results of the REMORA study, lenvatinib deserves to be a treatment option for patients with unresectable thymic carcinoma previously treated with platinum-based chemotherapy regimens.

There are no clinical study data on the efficacy and safety of lenvatinib in patients with chemotherapy-naïve unresectable thymic carcinoma, a patient population ineligible for the REMORA study. However, given the observations below, lenvatinib treatment is also allowable in patients with chemotherapy-naïve unresectable thymic carcinoma. Therefore, instead of restricting the use of lenvatinib to those previously treated with chemotherapy in the "Indications" section, the package insert should give caution in its "Precautions Concerning Indications" section that the efficacy and safety of lenvatinib in patients with chemotherapy-naïve unresectable thymic carcinoma have not been established, with information about the patient population in the REMORA study provided in the "Clinical Studies" section.

- In the Japanese clinical practice guidelines, carboplatin plus paclitaxel combination chemotherapy is recommended as a treatment option for patients with chemotherapy-naïve unresectable thymic carcinoma. The response rate of the combination therapy was 36% in patients receiving carboplatin plus paclitaxel therapy in a Japanese phase II study (*Lung Cancer*. 2010;67:194-7), which is comparable to the response rate obtained in the REMORA study that targeted patients who had been previously treated with carboplatin plus paclitaxel combination chemotherapy.
- The pharmacology of carboplatin and paclitaxel differs from that of lenvatinib, and it is unlikely a prior use of carboplatin plus paclitaxel chemotherapy will influence the efficacy of lenvatinib.

There are no clinical study data evaluating the efficacy and safety of lenvatinib used as neoadjuvant or adjuvant chemotherapy. Therefore, lenvatinib is not recommended for neoadjuvant or adjuvant chemotherapy.

Based on the above, it is appropriate to define the indication as "unresectable thymic carcinoma," with the following cautionary statements presented in the "Precautions Concerning Indications" section.

- The efficacy and safety of lenvatinib in patients with chemotherapy-naïve thymic carcinoma have not been established.
- The efficacy and safety of lenvatinib as neoadjuvant or adjuvant chemotherapy have not been established.

PMDA's view:
The applicant's explanation is generally acceptable. However, given the limited options in approved drugs indicated for thymic carcinoma and the rarity of the disease in Japan, it is more appropriate to communicate the characteristics of patients enrolled in the REMORA study via the "Clinical Studies" section of the package insert, with the cautionary statements below in the "Precautions Concerning Indications" section, rather than providing caution against unestablished efficacy and safety of lenvatinib in patients with chemotherapy-naïve thymic carcinoma. The indication should be "unresectable thymic carcinoma" as proposed by the applicant.

The Japanese clinical practice guidelines on the treatment of thymic carcinoma recommend neoadjuvant therapy as a treatment option but do not mention adjuvant therapy, indicating that adjuvant therapy is not recommendable. Based on this, etc., lenvatinib is unlikely to be used as adjuvant therapy. It is thus not necessary to highlight that the efficacy and safety of lenvatinib in adjuvant therapy have not been established.

- The efficacy and safety of lenvatinib as neoadjuvant chemotherapy have not been established.
- Eligible patients should be selected based on a thorough understanding of the efficacy and safety of lenvatinib as well as the information described in the "Clinical Studies" section.

7.R.4 Dosage and administration

Initially, the proposed dosage and administration of lenvatinib for the present application was "The usual adult dosage is 24 mg of lenvatinib administered orally once daily. The dose may be reduced according to the patient's condition," which was identical to that of the approved indication for the treatment of thyroid cancer. The proposed "Precautions Concerning Dosage and Administration" section for the present application was also the same as that of the approved indication for the treatment of thyroid cancer. However, after the submission of partial change application, the applicant explained that the contents of the "Precautions Concerning Dosage and Administration" section would be modified as follows [see Section 7.R.3]:

- The efficacy and safety of concomitant use of lenvatinib with the other antineoplastic drugs have not been established.
- The efficacy and safety of lenvatinib in combination with radiotherapy have not been established.
- Criteria for dose reduction, interruption, and treatment discontinuation of lenvatinib in the event of adverse drug reactions

On the basis of the discussions in the following subsections and in Sections "7.R.1 Efficacy" and "7.R.2 Safety," PMDA concluded that it is appropriate to define the dosage and administration of lenvatinib as "The usual adult dosage is 24 mg of lenvatinib administered orally once daily. The dose may be reduced according to the patient's condition," as proposed by the applicant, with the following descriptions presented in the "Precautions Concerning Dosage and Administration" section:

- The efficacy and safety of concomitant use of lenvatinib with the other antineoplastic drugs have not been established.
- Criteria for dose reduction, interruption, and treatment discontinuation of lenvatinib in the event of adverse drug reactions

7.R.4.1 Dosage regimen of lenvatinib

The applicant's explanation about the rationale for the proposed dosage and administration of lenvatinib in patients with unresectable thymic carcinoma:

The dosage regimen and dose modification criteria in the REMORA study were the same as those for the approved indication for the treatment of thyroid cancer. The study demonstrated the clinical benefit of lenvatinib in patients with unresectable thymic carcinoma. Accordingly, the proposed dosage regimen and the dose modification criteria were specified based on those of the REMORA study.

Radiotherapy has been employed for thymic carcinoma based on the radiotherapy treatment modality for lung cancer. However, taking into account of the likelihood of increased risks of hemorrhage associated with angiogenesis inhibitors including lenvatinib, it is unlikely that the combination of lenvatinib and radiotherapy will commonly be used in the treatment of unresectable thymic carcinoma. Nevertheless, there are currently no clinical study data on the efficacy and safety of lenvatinib used radiotherapy or with other antineoplastic drugs, and this will be highlighted in the "Precautions Concerning Dosage and Administration" section. Patients with prior chemoradiotherapy were also eligible for the REMORA study, and there were no trends towards increasing hemorrhage-related risks in these patients.

PMDA's view:
The applicant's explanation above is generally acceptable. However, the cautionary statement about the use of lenvatinib in combination with radiotherapy is not necessary because it is unlikely that the combination of lenvatinib and radiotherapy will actively be used based on the following points, etc:

- The clinical practice guidelines on the treatment of thymic carcinoma published in Japan and other countries have no descriptions about lenvatinib or other angiogenesis inhibitors used in combination with radiotherapy, indicating that such treatment is not recommended.
- The safety of lenvatinib used in combination with radiotherapy in patients with thymic carcinoma has not been evaluated in the REMORA study, etc.

7.R.5 Post-marketing investigations

Based on the findings including a high incidence of decreased thyroid function in the REMORA study [see Section 7.R.2.2], the applicant plans to conduct post-marketing surveillance to investigate the occurrence of decreased thyroid function in the clinical use of lenvatinib in patients with unresectable thymic carcinoma.

PMDA's view:
Despite the increasing amount of post-marketing safety data of lenvatinib available from patients with the approved indications, safety data of lenvatinib from patients with unresectable thymic carcinoma remain insufficient. Given the circumstances, post-marketing surveillance should be conducted involving patients with unresectable thymic carcinoma, and obtained safety data should be promptly provided to healthcare professionals. Based on the discussion in Section "7.R.2 Safety," the safety specification should be "decreased thyroid function," and its occurrence, etc. in the post-marketing setting should be investigated. The details of surveillance including the data collection methodology should be further discussed.

7.2 Adverse events, etc. observed in the clinical study

The section below discusses the main adverse events from the results of the clinical study submitted, except for those that resulted in death, which are discussed in Section "7.1 Evaluation data."

7.2.1 Japanese phase II study (REMORA study)

Adverse events occurred in 42 of 42 subjects (100%). Adverse events for which a causal relationship to lenvatinib could not be ruled out also occurred in all subjects. Table 7 shows adverse events occurring in ≥20% of subjects.

Table 7. Adverse events occurring in ≥20% of subjects

SOC PT (MedDRA/J ver.19.1)	n (%) N = 42 All Grades	 Grade ≥3
All adverse events	42 (100)	37 (88.1)
Endocrine disorders		
Hypothyroidism	27 (64.3)	0
Gastrointestinal disorders		
Diarrhoea	24 (57.1)	4 (9.5)
Stomatitis	14 (33.3)	0
Nausea	12 (28.6)	0
Vomiting	10 (23.8)	0
General disorders and administration site conditions		
Malaise	14 (33.3)	0
Fatigue	12 (28.6)	0
Investigations		
Platelet count decreased	23 (54.8)	2 (4.8)
Weight decreased	17 (40.5)	3 (7.1)
AST increased	14 (33.3)	1 (2.4)
ALT increased	12 (28.6)	0
Metabolism and nutrition disorders		
Decreased appetite	18 (42.9)	1 (2.4)
Hypoalbuminaemia	11 (26.2)	0
Nervous system disorders		
Headache	12 (28.6)	0
Renal and urinary disorders		
Proteinuria	30 (71.4)	0
Respiratory, thoracic and mediastinal disorders		
Dysphonia	17 (40.5)	0
Skin and subcutaneous tissue disorders		
Palmar-plantar erythrodysaesthesia syndrome	29 (69.0)	3 (7.1)
Vascular disorders		
Hypertension	37 (88.1)	27 (64.3)

Serious adverse events occurred in 12 of 42 subjects (28.6%). These serious adverse events were abdominal pain, abdominal pain upper, decreased appetite, diarrhoea, electrocardiogram T wave abnormal, large intestine perforation, left ventricular dysfunction, pericardial effusion, pneumonia, pneumonitis, pneumothorax, and urinary tract infection (1 subject each, 2.4%). A causal relationship to lenvatinib could not be ruled out for abdominal pain, abdominal pain upper, decreased appetite, electrocardiogram T wave abnormal, large intestine perforation, left ventricular dysfunction, and pneumonitis (1 subject each).

Adverse events led to treatment discontinuation of lenvatinib in 4 of 42 subjects (9.5%). These adverse events were large intestine perforation, left ventricular dysfunction, pneumonitis, and pneumothorax (1 subject each, 2.4%), and a causal relationship to lenvatinib could not be ruled out for large intestine perforation, left ventricular dysfunction, and pneumonitis (1 subject each).

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 investigation is currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

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

The investigation is currently underway. The results and conclusion by PMDA 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 a certain level of efficacy in the treatment of unresectable thymic carcinoma, and that lenvatinib has acceptable safety in view of its benefits. Lenvatinib is clinically meaningful because it offers a new treatment option for patients with unresectable thymic carcinoma. PMDA considers that several issues including the indications, dosage and administration, and post-marketing investigation are subject to further discussion.

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

Review Report (2)

January 29, 2021

Product Submitted for Approval

Brand Name	Lenvima Capsules 4 mg Lenvima Capsules 10 mg
Non-proprietary Name	Lenvatinib Mesilate
Applicant	Eisai Co., Ltd.
Date of Application	July 30, 2020

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 below. 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

In the REMORA study in patients with unresectable thymic carcinoma previously treated with platinum-based chemotherapy regimens, the primary endpoint of the response rate by independent central review according to RECIST ver.1.1 and the 90% CI was 38.1% [25.6, 52.0] (16 of 42 subjects).

As discussed in Section "7.R.1 Efficacy" of Review Report (1), the lower limit of 90% CI for the response rate in the REMORA study exceeded the prespecified response rate threshold of 10%, and no standard therapy has demonstrated to improve OS in the target patient population for the study. Given these, PMDA concluded that lenvatinib has promising efficacy in patients with unresectable thymic carcinoma previously treated with platinum-based chemotherapy regimens.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion.

1.2 Safety

PMDA's conclusions

In view of the discussion in Section "7.R.2 Safety" in Review Report (1), adverse events that require caution in the use of lenvatinib in patients with unresectable thymic carcinoma previously treated with platinum-based chemotherapy regimens are those events found to warrant caution during the approval process of lenvatinib for

the previously approved indications (i.e., hypertension/hypertensive crisis, infections, renal disorder, haemorrhage-related events, palmar-plantar erythrodysaesthesia syndrome, haematotoxicity, liver disorder, acute cholecystitis, arrhythmia, cardiac function disturbance, hypocalcaemia, thromboembolism, gastrointestinal perforation, gastrointestinal fistulae, pneumothorax, posterior reversible encephalopathy syndrome, delayed wound healing, interstitial lung disease, and blood thyroid stimulating hormone increased) as well as newly added decreased thyroid function. Caution should be exercised against these adverse events during treatment with lenvatinib.

Although the use of lenvatinib requires caution against the above-mentioned adverse events, PMDA concluded that patients with thymic carcinoma will be tolerant to lenvatinib as long as they are followed up by physicians with sufficient knowledge and experience in cancer chemotherapy appropriately through adverse event monitoring and control and dose interruption or reduction.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

1.3 Clinical positioning and indications

In view of the discussion in Section "7.R.3 Clinical positioning and indications" in Review Report (1), PMDA concluded that it is appropriate to define the indication as "unresectable thymic carcinoma" as proposed by the applicant, with information about the characteristics of patients enrolled in the REMORA study provided in the "Clinical Studies" section and the following cautionary statements in the "Precautions Concerning Indications" section of the package insert.

Precautions Concerning Indications

- The efficacy and safety of lenvatinib as neoadjuvant chemotherapy have not been established.
- Eligible patients should be selected based on a thorough understanding of the efficacy and safety of lenvatinib as well as the information described in the "Clinical Studies" section.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion.

Based on the above, PMDA instructed the applicant to define the "Indications" and "Precautions Concerning Indications" sections as described above, and the applicant agreed.

1.4 Dosage and administration

In view of the discussion in Section "7.R.4 Dosage and administration" in Review Report (1), PMDA concluded that it is appropriate to define the dosage and administration of lenvatinib as "The usual adult dosage is 24 mg of lenvatinib administered orally once daily. The dose may be reduced according to the patient's condition," as proposed by the applicant, with the following cautionary statements provided in the "Precautions Concerning Dosage and Administration" section:

Precautions Concerning Dosage and Administration

- The efficacy and safety of concomitant use of lenvatinib with the other antineoplastic drugs have not been established.
- Criteria for dose reduction, interruption, and treatment discontinuation of lenvatinib in the event of adverse drug reactions

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

Based on the above, PMDA instructed the applicant to specify the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections as described above, and the applicant agreed.

1.5 Risk management plan (draft)

Based on the high incidence of decreased thyroid function, etc. in the REMORA study, the applicant plans to conduct post-marketing surveillance for the investigation of the occurrence of decreased thyroid function in the clinical use of lenvatinib in patients with unresectable thymic carcinoma.

In view of the discussion in Section "7.R.5 Post-marketing investigations" in Review Report (1), PMDA concluded that post-marketing surveillance should be conducted involving patients with unresectable thymic carcinoma receiving lenvatinib, and obtained safety data should be provided to healthcare professionals promptly. PMDA also concluded as follows about the post-marketing surveillance plan:

- Based on the discussion in Section "7.R.2 Safety," the safety specification should be "decreased thyroid function," to investigate the occurrence, etc of the event in the post-marketing setting.
- In terms of data collection methodology, data related to decreased thyroid function associated with lenvatinib treatment are available through an existing database. Post-marketing surveillance in patients with unresectable thymic carcinoma should be thus conducted as a post-marketing database study so as to collect relevant data through the database study.

At the Expert Discussion, the expert advisors supported the PMDA's conclusions.

Accordingly, PMDA instructed the applicant to review the post-marketing surveillance plan. The applicant responded as follows:

- Utilizing an existing database through which data related to lenvatinib-associated decreased thyroid function are available, the post-marketing surveillance will be conducted as a post-marketing database study for the investigation of the occurrence, etc. of decreased thyroid function in patients with unresectable thymic carcinoma after verifying its feasibility.
- The safety specification for the survey will be decreased thyroid function. The occurrence, etc. of the event following lenvatinib treatment in patients with unresectable thymic carcinoma will be investigated.

PMDA accepted the applicant's explanation.

Based on the discussions above and in Section "7.R.2 Safety" in Review Report (1), PMDA concluded that the risk management plan (draft) for lenvatinib should include the safety specifications presented in Table 8, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 9.

Table 8. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hypertension • Hemorrhage (including carotid artery hemorrhage associated with tumor size reduction or necrosis and tumor hemorrhage) • Arterial thromboembolism • Venous thromboembolism • Liver disorder • Acute cholecystitis • Renal disorder • Gastrointestinal perforation, gastrointestinal fistulae, pneumothorax • Posterior reversible encephalopathy syndrome • Cardiac disorder • Hand and foot syndrome • Infections • Hematotoxicity • Hypocalcemia • Delayed wound healing • Interstitial lung disease • Decreased thyroid function	None	None
Efficacy specification		
None		

Underline denotes addition.

Table 9. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Specified use-results survey in patients with unresectable hepatocellular carcinoma • Post-marketing database survey in patients with unresectable thymic carcinoma (decreased thyroid function) • Post-marketing clinical study (extension study of Study E7080-G000-303)	• Post-marketing clinical study (extension study of Study E7080-G000-303)	• Preparation and provision of materials for healthcare professionals (proper use guide [unresectable thyroid cancer]) • Preparation and provision of materials for healthcare professionals (proper use guide [unresectable hepatocellular carcinoma]) • Preparation and provision of materials for healthcare professionals (proper use guide [unresectable thymic carcinoma])

Underline denotes additions for the new indication.

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 Products Including Pharmaceuticals and Medical Devices. 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 5.3.5.2.1, 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 Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall evaluation

As a result of the above review, PMDA has concluded that lenvatinib may be approved for the indications and dosage and administration presented below with the following approval condition, presupposing the provision of appropriate cautionary advice via the package insert and of information on the proper use of the product in the post-marketing setting, as well as the proper use of the product under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy and at medical institutions well equipped for emergency care. Lenvatinib is designated as an orphan drug for the intended indication of "unresectable thymic carcinoma," thus the re-examination period for the new indication should be 10 years.

Indications (Underline denotes additions)

(1) Lenvima Capsules 4 mg

Unresectable thyroid cancer, unresectable hepatocellular carcinoma, unresectable thymic carcinoma

(2) Lenvima Capsules 10 mg

Unresectable thyroid cancer, unresectable thymic carcinoma

Dosage and Administration (Underline denotes additions)

(1) Lenvima Capsules 4 mg

Unresectable thyroid cancer, unresectable thymic carcinoma

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.

(2) Lenvima Capsules 10 mg

Unresectable thyroid cancer, unresectable thymic carcinoma

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

Approval Condition

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 Concerning Indications (Underline denotes additions)

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

3. 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.
4. 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.

Unresectable thymic carcinoma

5. The efficacy and safety of lenvatinib as neoadjuvant chemotherapy have not been established.
6. Eligible patients should be selected based on a thorough understanding of the efficacy and safety of lenvatinib as well as the information described in the "Clinical Studies" section.

Precautions Concerning Dosage and Administration (Underline denotes additions)

All indications

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

Unresectable thyroid cancer, unresectable thymic carcinoma

2. 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 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 level 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.

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

Unresectable hepatocellular carcinoma

3. 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.
4. 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.
Hematotoxicity 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 decreased thyroid function, 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 decreased thyroid function, 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.

* Graded in accordance with CTCAE version 4.0

Appendix

List of Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
CR	complete response
FGFR	fibroblast growth factor receptor
HCl	hydrochloric acid
KIT	a stem cell growth factor receptor
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
OS	overall survival
PD	progressive disease
PDGFR	platelet-derived growth factor receptor
PR	partial response
PT	preferred term
QD	quaque die
RECIST	Response Evaluation Criteria in Solid Tumors
REMORA study	Study NCCH1508
RET	rearranged during transfection
SD	stable disease
SOC	system organ class
VEGFR	vascular endothelial growth factor receptor
Study 201	Study E7080-G000-201
Study 202	Study E7080-J081-202
Study 208	Study E7080-J081-208
Study 303	Study E7080-G000-303
Study 304	Study E7080-G000-304
Partial change application	Application for partial change approval
PMDA	Pharmaceuticals and Medical Devices Agency
Japanese clinical practice guidelines	Guidelines for Diagnosis and Treatment of Lung Cancer 2018: Thymic Carcinoma [in Japanese], the Japan Lung Cancer Society
platinum-based chemotherapy regimen	carboplatin or cisplatin
Lenvatinib	Lenvatinib mesilate