Medical & Education Training

Lenvatinib SELECT Trial

Differentiated Thyroid Carcinoma

Review of Select Adverse Reactions

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human health care

Updated to June 2024: Lenvima® [package insert]. Nutley, NJ: Eisai Inc.

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Adverse Reaction *(listed in alphabetical order)*	SELECT Protocol	SELECT Safety Results
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Proteinuria	Protocol Management	Safety Summary & PI Management
Stomatitis	Protocol Management	Safety Summary & PI Management

Table of Abbreviations

Abbreviation	Definition
ACE	Angiotensin-converting enzyme
ADL	Activity of daily living
AE	Adverse event
AR	Adverse reaction
ARB	Angiotensin receptor blockers
BP	Blood pressure
CTCAE	Common terminology criteria for adverse events
DBP	Diastolic blood pressure
DTC	Differentiated thyroid carcinoma
NCI	National Cancer Institute
PI	Prescribing information
PO	Taken orally
PPE	Palmar-plantar erythrodysesthesia
QD	Once daily
RAI-rDTC	Radioactive iodine-refractory differentiated thyroid carcinoma
SBP	Systolic blood pressure
TEAE	Treatment-emergent adverse event
TPN	Total parenteral nutrition
WNL	Within normal limits

Select ARs Observed with Lenvatinib

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

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Grading of Adverse Reactions

Common Terminology Criteria for Adverse Events (CTCAE)

- *The NCI Common Terminology Criteria for Adverse Events (CTCAE) is a descriptive terminology that provides a grading (severity) scale for an AE Term, which can be utilized for Adverse Event (AE) reporting*
- *The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for an AE term based on the general guideline shown below*
- *Adverse reactions listed on the label may include various preferred terms as reported in the trial; however, the CTCAE doesn't include a matching AE Term for all Preferred Terms*
- *CTCAE Term or General Guideline used for grading was at the discretion of the investigators*

CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
General Guideline	• *Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only intervention not indicated*	• *Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*	• *Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL*	• *Life-threatening consequences; urgent intervention indicated*	• *Death related to AE*

Activities of Daily Living (ADL)	
Instrumental ADL	**Self care ADL**
• *Refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*	• *Refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden*

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. NCI CTCAE Version 4.0 Published May 28, 2009.

SELECT: Study 303: Phase 3 Study of Lenvatinib in RAI-R DTC

Most Common Adverse Reactions

Most common ARs (≥30%)[a]	n=261
Hypertension	73%
Fatigue	67%
Diarrhea	67%
Arthralgia/myalgia	62%
Decreased appetite	54%
Decreased weight	51%
Nausea	47%
Stomatitis	41%
Headache	38%
Vomiting	36%
Proteinuria	34%
PPE	32%
Abdominal pain	31%
Dysphonia	31%

Most common serious ARs (≥2%)[a]	n=261
Pneumonia	4%
Hypertension	3%
Dehydration	3%

a. In lenvatinib-treated patients (in order of decreasing frequency).

- SELECT randomized (2:1) patients with RAI-R DTC to lenvatinib (n=261) or placebo (n=131)
- Among 261 patients who received lenvatinib, median age was 64 years, 52% were females, 80% were White, 18% were Asian, and 2% were Black; and 4% were Hispanic/Latino

Median duration of treatment for lenvatinib	n=261
16.1 months	

Dose reductions due to ARs	n=261
Lenvatinib 24 mg	68%

Discontinuations due to ARs	n=261
Lenvatinib 24 mg	18%

Most common ARs (≥10%) resulting in lenvatinib dose reductions[a]	n=261
Hypertension	13%
Proteinuria	11%
Decreased appetite	10%
Diarrhea	10%

Most common ARs (≥1%) resulting in lenvatinib discontinuation[a]	n=261
Hypertension	1%
Asthenia	1%

** Refer to next slide for preferred terms included in adverse reaction definition*

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1. Lenvima® [package insert]. Nutley, NJ: Eisai Inc.

SELECT: Study 303: Phase 3 Study of Lenvatinib in RAI-R DTC

Adverse Events Included in Each Adverse Reaction by Preferred Term

- **ARs (grouped preferred terms per FDA definitions) were applied in accordance with the FDA prescribing information (PI) for lenvatinib**

AR *(listed in alphabetical order)*	CMQ preferred terms included
Abdominal pain	• Abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, GI pain
Arthralgia/Myalgia	• Musculoskeletal pain, back pain, pain in extremity, arthralgia, myalgia
Decreased appetite	• Decreased appetite
Diarrhea	• Diarrhea
Fatigue	• Asthenia, fatigue, malaise
Headache	• Headache
Hypertension	• Hypertension, hypertensive crisis, increased BP diastolic, increased BP
Nausea	• Nausea
PPE	• PPE
Proteinuria	• Proteinuria
Stomatitis	• Aphthous stomatitis, stomatitis, glossitis, mouth ulceration, and mucosal inflammation
Vomiting	• Vomiting
Weight decreased	• Weight decreased

This is a post-hoc exploratory analysis for descriptive purpose only.

1. Lenvima® [package insert]. Nutley, NJ: Eisai Inc.

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SELECT: Study 303: Phase 3 Study of Lenvatinib in RAI-R DTC

Post-hoc Analysis of Time to First Onset of Most Common ARs Leading to Dose Reduction or Interruption of Lenvatinib (≥5%) (n=261)

AR	Incidence[b] n	Incidence[b] %	Lenvatinib Dose Interruption[c]	Lenvatinib Dose Reduction[c]	Lenvatinib Dose Discontinuation[c]	Median time to first onset (weeks)[a]	Max
Hypertension[d]	190	73%	13%	13%	1%	MIN: 0.1 / Q1: 1.4 / Median: 2.3 / Q3: 5.0 / MAX: 80.1 weeks	80.1
Fatigue[e]	175	67%	17%	13%	2%	MIN: 0.1 / Q1: 1.1 / Median: 3.0 / Q3: 7.3 / MAX: 92.3 weeks	92.3
Headache	100	38%	3%	4%	0%	MIN: 0.1 / Q1: 0.9 / Median: 3.1 / Q3: 11.8 / MAX: 74.1 weeks	74.1
Arthralgia/Myalgia[f]	162	62%	6%	5%	0%	MIN: 0.1 / Q1: 1.4 / Median: 3.8 / Q3: 12.9 / MAX: 93.7 weeks	93.7
Stomatitis[g]	107	41%	7%	7%	1%	MIN: 0.1 / Q1: 1.6 / Median: 4.0 / Q3: 12.0 / MAX: 87.0 weeks	87.0
Decreased Appetite	142	54%	13%	10%	0%	MIN: 0.1 / Q1: 1.1 / Median: 4.2 / Q3: 15.0 / MAX: 73.3 weeks	73.3
PPE	84	32%	10%	8%	0%	MIN: 0.4 / Q1: 3.1 / Median: 5.9 / Q3: 12.1 / MAX: 39.1 weeks	39.1
Abdominal Pain[h]	82	31%	5%	2%	0%	MIN: 0.1 / Q1: 2.9 / Median: 6.3 / Q3: 19.6 / MAX: 84.1 weeks	84.1
Proteinuria	88	34%	17%	11%	1%	MIN: 0.7 / Q1: 4.0 / Median: 7.7 / Q3: 19.1 / MAX: 114.1 weeks	114.1
Nausea	122	47%	11%	6%	0%	MIN: 0.1 / Q1: 1.6 / Median: 7.8 / Q3: 20.1 / MAX: 78.9 weeks	78.9
Weight Decreased	134	51%	10%	8%	0%	MIN: 0.1 / Q1: 8.0 / Median: 12.1 / Q3: 20.1 / MAX: 96.0 weeks	96.0
Diarrhea	176	67%	18%	10%	0%	MIN: 0.1 / Q1: 4.6 / Median: 13.1 / Q3: 26.7 / MAX: 94.0 weeks	94.0
Vomiting	93	36%	6%	4%	0%	MIN: 0.1 / Q1: 5.9 / Median: 13.7 / Q3: 26.9 / MAX: 94.0 weeks	94.0

a. Median time to first onset in patients that experience the AR
b. All Grades
c. Percentages are based on the total number of patients
d. Includes hypertension, hypertensive crisis, increased DBP, and increased BP
e. Includes asthenia, fatigue, and malaise
f. Includes musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia
g. Includes aphthous stomatitis, stomatitis, glossitis, mouth ulceration, and mucosal inflammation
h. Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal pain

This is a post-hoc exploratory analysis for descriptive purpose only

1. Eisai Stats Report: LEN303MSL-ARMGM: 23 JUL 2020.

Hypertension

SELECT Study Results and Lenvatinib PI Recommendations: Hypertension

HYPERTENSION[a]	Lenvatinib (n=261)[1]									
	INCIDENCE						ONSET	MANAGEMENT		
								Dose Modifications		Discontinuation
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades	Median Time to First Onset[b]	Lenvatinib Dose Interruption	Lenvatinib Dose Reduction	Lenvatinib
	6%	22%	44%	0%	0%	73%	2.3 weeks	13%	13%	1%

a. This is a post-hoc exploratory analysis for descriptive purpose only; no conclusion can be drawn; b. Median time to first onset in the 190 patients that experienced hypertension.

Lenvatinib PI Recommendations[2]

Prior to initiating lenvatinib:

- Control blood pressure

Monitor blood pressure:

- After 1 week
- Then every 2 weeks for the first 2 months
- And then at least monthly thereafter during treatment

For Grade 3 hypertension
(SBP ≥160 mm Hg or DBP ≥100 mm Hg)
that persists despite optimal hypertensive therapy

↓

Withhold lenvatinib

↓

When hypertension is controlled at
≤ Grade 2
(SBP 140–159 mm Hg ; DBP 90–99mm Hg)

↓

Resume lenvatinib at reduced dose

For Grade 4 hypertension

↓

Permanently discontinue lenvatinib

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1. Eisai Stats Report: LEN303MSL-ARMGM: 23 JUL 2020
2. Lenvima® [package insert]. Nutley, NJ: Eisai Inc.

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Grading: Hypertension

Preferred Terms Included & Related NCI CTCAE v4.0 Terms

Preferred Term *(Listed in alphabetical order)*	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypertension	*Hypertension*	• *Systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg*	• *Systolic BP 140–159 mm Hg or diastolic BP 90–99 mm Hg; medical intervention indicated; recurrent or persistent (≥24hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated*	• *Systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated*	• *Life-threatening consequences; urgent intervention indicated*	• *Death*
Hypertensive crisis	*Not listed in CTCAE*	***CTCAE Term or General Guideline used for grading was at the discretion of the investigators***				
Increased BP						
Increased diastolic BP						

	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	General Guideline	• *Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only intervention not indicated*	• *Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*	• *Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL*	• *Life-threatening consequences; urgent intervention indicated*	• *Death related to AE*

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1. NCI CTCAE Version 4.0 Published May 28, 2009.

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SELECT Study Protocol: Management of Lenvatinib Related Hypertension

Blood Pressure Monitoring

BP Monitoring:

- Early detection and effective management of hypertension were important to minimize the need for lenvatinib dose interruptions and reductions
- BP assessments during the Treatment Period were required at:

Cycles 1 and 2	Cycle 3 and Subsequent Cycles	Off-treatment Visit
▪ Day 1 and Day 15	▪ Day 1[a] *a. Note: for patients with SBP ≥160 mm Hg or DBP ≥100 mm Hg, BP assessment was also required on Day 15 (or more frequently as clinically indicated)* • *Until SBP had been ≤150 mm Hg and DBP had been ≤95 mm Hg for 3 consecutive months*	

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1. Protocol E7080-G000-303; 10 Apr 2012; Pages 42, 68–72.

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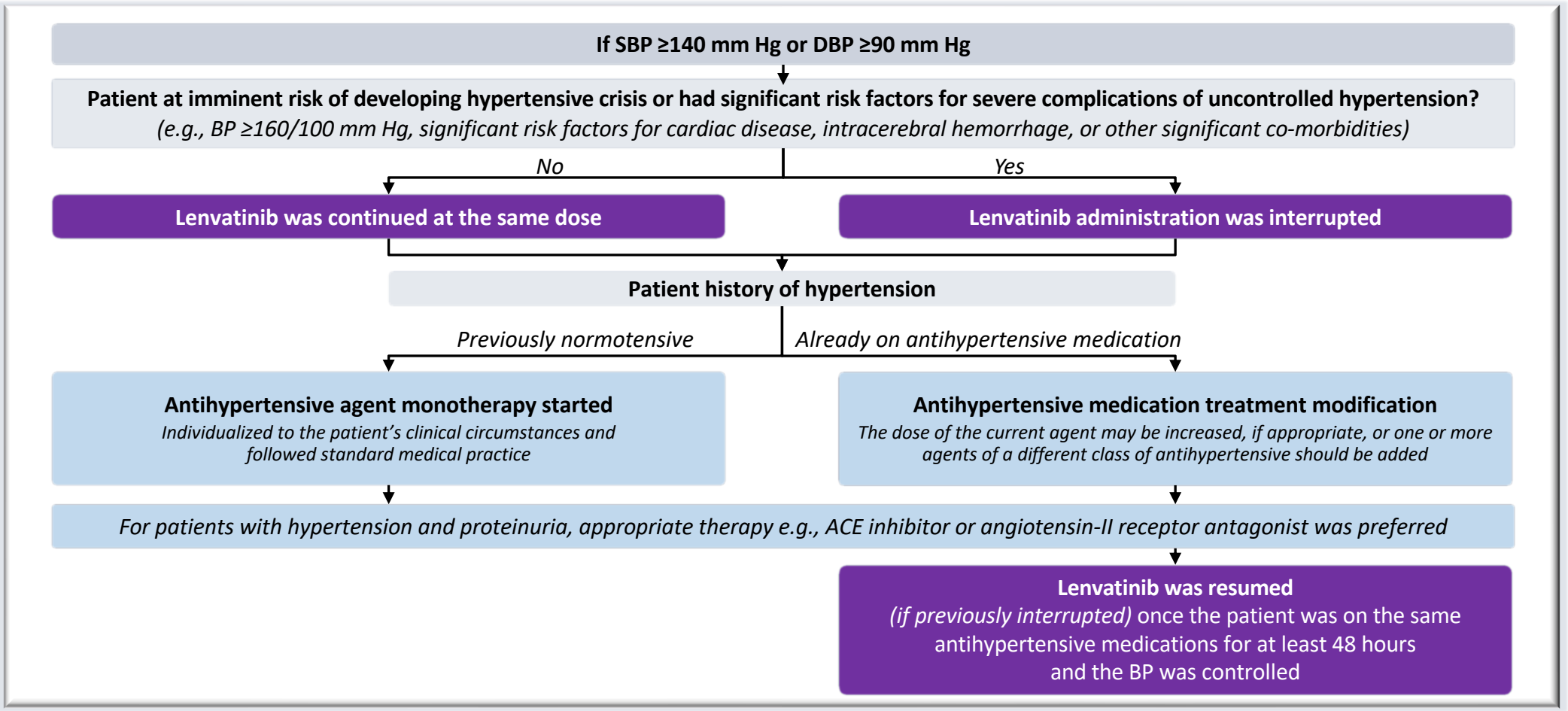
SELECT Study Protocol: Management of Lenvatinib Related Hypertension

- ***Patients were required to have adequately controlled BP with or without antihypertensive medications, defined as BP ≤150/90 mm Hg at screening and no change in antihypertensive medications within 1 week prior to the Cycle 1/Day 1***



NOTE: *i) One BP assessment was defined as the mean value of 3 measurements at least 5 minutes apart. ii) BP was confirmed on 2 assessments 1 hour apart. iii) If SBP ≥160 mm Hg or DBP ≥100 mm Hg BP was monitored every 2 weeks (on Day 15 or more frequently as clinically indicated) until SBP was ≤150 mm Hg and DBP was ≤95 mm Hg for 3 consecutive months*

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1. Protocol E7080-G000-303; 10 Apr 2012; Pages 37 and 42.

SELECT Study Protocol: Management of Lenvatinib Related Hypertension

If SBP ≥160 mm Hg or DBP ≥100 mm Hg persisted despite maximal hypertensive therapy
(either by dose increase or the addition of a different class of antihypertensive)

↓

Lenvatinib administration was interrupted

↓

When **SBP ≤150 mm Hg and DBP ≤95 mm Hg**
and
the patient was on a stable dose of antihypertensive medication for at least 48 hours

↓

Lenvatinib administration was restarted at a lower dose (one dose level reduction)[a]

For Grade 4 hypertension

↓

Lenvatinib was discontinued and appropriate medical management instituted

***a**. Once the dose was reduced, it was not increased at a later date.*

***NOTE:** i) One BP assessment was defined as the mean value of 3 measurements at least 5 minutes apart. ii) BP was confirmed on 2 assessments 1 hour apart. iii) If SBP ≥160 mm Hg or DBP ≥100 mm Hg BP was monitored every 2 weeks (on Day 15 or more frequently as clinically indicated) until SBP was ≤150 mm Hg and DBP was ≤95 mm Hg for 3 consecutive months*

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1. Protocol E7080-G000-303; 10 Apr 2012; Pages 42–43.

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SELECT Study Protocol: Management of Lenvatinib Related Hypertension

Management of Hypertension: Dose Reductions for Adverse Reactions

- Dose reductions occurred in succession based on the previous dose level

Recommended dose	First dosage reduction to	Second dosage reduction to	Third dosage reduction to	Fourth dosage reduction to
24 mg once daily	20 mg once daily	14 mg once daily	10 mg once daily	Discussed with Sponsor

If SBP ≥160 mm Hg or DBP ≥100 mm Hg recurred on the 10 mg QD dose despite optimal management of hypertension with antihypertensive medications then lenvatinib administration was interrupted and a restart of study medication was discussed with the sponsor

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. Protocol E7080-G000-303; 10 Apr 2012; Pages 45.

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SELECT Study Results: Hypertension

Concomitant Antihypertensive Medications[a, b, c]

Data cut-off: November 15, 2013

	Lenvatinib (n=261)
Patients who took ≥1 concomitant antihypertensive medication	**84.3%**
Diuretics	
High-ceiling diuretics	6.1%
Potassium-sparing agents	3.1%
Low-ceiling diuretics (thiazides)	18.8%
Low-ceiling diuretics (excluding thiazides)	4.6%
Calcium channel blockers	
Selective calcium channel blockers with mainly vascular effects	55.9%
Selective calcium channel blockers with direct cardiac effects	2.7%
Beta blocking agents	**25.7%**
Angiotensin II antagonists	**28.0%**
ACE inhibitors	**41.0%**
Combination agents	
Angiotensin II antagonists (combinations)	9.2%
ACE inhibitors (combinations)	6.9%
Diuretics and potassium-sparing agents in combination	2.7%
Beta blocking agents and other diuretics	0.4%
Beta blocking agents and thiazides	0.4%
Antiadrenergic agents	
Antiadrenergic agents (peripherally acting)	6.5%
Antiadrenergic agents (centrally acting)	5.0%
Arteriolar smooth muscle acting agents (hydralazine or minoxidil)	**2.3%**
Vasodilators used in cardiac diseases	**1.9%**
Other antihypertensives	**≤3.1%[d]**

a. Analysis of all patients in the full-analysis set.

b. For patients with hypertension and proteinuria, treatment with an ACE inhibitor or ARB was preferred.[2]

c. Concomitant medications were defined as medications that started before the first dose of study drug and were continuing at the time of the first dose of study drug, or started on or after the date of the first dose of study drug up to 30 days after the patient's last dose. Data should be interpreted with caution as concomitant medications used for a specific AE is not available.

d. Patients receiving other concomitant antihypertensive medications may have been counted more than once.

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1. *Protocol E7080-G000-303; 10 Apr 2012; Pages 45.*
2. *CSR E7080-G000-303; 05 Jun 2014; Table 14.1.6.4.*

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Fatigue

SELECT Study Results and Lenvatinib PI Recommendations: Fatigue

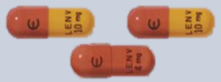
FATIGUE[a]	Lenvatinib (n=261)[1]							
	INCIDENCE				ONSET	MANAGEMENT		
						Dose Modifications		Discontinuation
	Grade 1	Grade 2	Grade 3	All Grades	Median Time to First Onset[b]	Lenvatinib Dose Interruption	Lenvatinib Dose Reduction	Lenvatinib
	32%	24%	11%	67%	3.0 weeks	17%	13%	2%

a. This is a post-hoc exploratory analysis for descriptive purpose only; no conclusion can be drawn; b. Median time to first onset in the 175 patients that experienced fatigue.

Lenvatinib PI Recommendations[2]

Severity	Dosage Modifications for Lenvatinib
Grade 2 fatigue that is persistent or intolerable **Grade 3** fatigue	▪ Withhold until improves to Grade 0 to 1 or baseline ▪ Resume at reduced dose

Dose Levels[2] *(Capsules pictured are not actual size)*

Recommended Dose of Lenvatinib		First Dosage Reduction To		Second Dosage Reduction To		Third Dosage Reduction To	
24 mg PO QD	 (two 10-mg capsules + one 4-mg capsule)	**20 mg** PO QD	 (two 10-mg capsules)	**14 mg** PO QD	 (one 10-mg capsule + one 4-mg capsule)	**10 mg** PO QD	 (one 10-mg capsule)

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1. *Eisai Stats Report: LEN303MSL-ARMGM: 23 JUL 2020*
2. *Lenvima® [package insert]. Nutley, NJ: Eisai Inc.*

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Grading: Fatigue

Preferred Terms Included & Related NCI CTCAE v4.0 Terms

Preferred Term *(Listed in alphabetical order)*	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Asthenia	*Not listed in CTCAE*	***CTCAE Term or General Guideline used for grading was at the discretion of the investigators***				
Fatigue	*Fatigue*	• *Fatigue relieved by rest*	• *Fatigue not relieved by rest; limiting instrumental ADL*	• *Fatigue not relieved by rest, limiting self care ADL*	-	-
Malaise	*Malaise*	• *Uneasiness or lack of well being*	• *Uneasiness or lack of well being; limiting instrumental ADL*	-	-	-

	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	General Guideline	• *Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only intervention not indicated*	• *Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*	• *Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL*	• *Life-threatening consequences; urgent intervention indicated*	• *Death related to AE*

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1. NCI CTCAE Version 4.0 Published May 28, 2009.

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SELECT Study Protocol: Fatigue

Management of Fatigue – Dose Adjustment

- Dose adjustment for management of lenvatinib toxicity, including fatigue, was done in accordance with the following instructions:

Treatment-Related Toxicity[a]	Management	Dose adjustment
Grade 1	Treatment was continued	No change
Grade 2 – tolerable[b]	Treatment was continued	No change
Grade 2 – intolerable[b]	**Treatment was interrupted[c]** ➢ until resolved to Grade 0–1 or baseline	**One-level dose reduction**
Grade 3	**Treatment was interrupted[c]** ➢ until resolved to Grade 0-1 or baseline	**One-level dose reduction**

- Dose reductions occurred in succession based on the previous dose level
  - ➢ Once the dose was reduced, it was not increased at a later date

Recommended dose	First dosage reduction to	Second dosage reduction to	Third dosage reduction to	Fourth dosage reduction to
24 mg once daily	20 mg once daily	14 mg once daily	10 mg once daily	Discussed with Sponsor

a. NCI CTCAE, version 4.0.
b. Grade 2 toxicities were determined to be tolerable or intolerable by both the patient and investigator.
c. An interruption of lenvatinib for more than 28 days (due to treatment-related toxicities) required a discussion with the sponsor before treatment was resumed.

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1. Protocol E7080-G000-303; 10 Apr 2012; Page 45.

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Headache

SELECT Study Results and Lenvatinib PI Recommendations: Headache

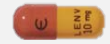
HEADACHE[a]	Lenvatinib (n=261)[1]							
	INCIDENCE				ONSET	MANAGEMENT		
						Dose Modifications		Discontinuation
	Grade 1	Grade 2	Grade 3	All Grades	Median Time to First Onset[b]	Lenvatinib Dose Interruption	Lenvatinib Dose Reduction	Lenvatinib
	25%	10%	3%	38%	3.1 weeks	3%	4%	0%

a. This is a post-hoc exploratory analysis for descriptive purpose only; no conclusion can be drawn; b. Median time to first onset in the 100 patients that experienced headache.

Lenvatinib PI Recommendations[2]

Severity	Dosage Modifications for Lenvatinib
Grade 2 headache that is persistent or intolerable **Grade 3** headache	▪ Withhold until improves to Grade 0 to 1 or baseline ▪ Resume at reduced dose

Dose Levels[2] *(Capsules pictured are not actual size)*

Recommended Dose of Lenvatinib		First Dosage Reduction To		Second Dosage Reduction To		Third Dosage Reduction To	
24 mg PO QD	 (two 10-mg capsules + one 4-mg capsule)	**20 mg** PO QD	 (two 10-mg capsules)	**14 mg** PO QD	 (one 10-mg capsule + one 4-mg capsule)	**10 mg** PO QD	 (one 10-mg capsule)

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1. *Eisai Stats Report: LEN303MSL-ARMGM: 23 JUL 2020*
2. *Lenvima® [package insert]. Nutley, NJ: Eisai Inc.*

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Grading: Headache

Preferred Terms Included & Related NCI CTCAE v4.0 Terms

Preferred Term *(Listed in alphabetical order)*	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Headache	*Headache*	• *Mild pain*	• *Moderate pain; limiting instrumental ADL*	• *Severe pain; limiting self care ADL*	-	-

	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	General Guideline	• *Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only intervention not indicated*	• *Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*	• *Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL*	• *Life-threatening consequences; urgent intervention indicated*	• *Death related to AE*

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1. NCI CTCAE Version 4.0 Published May 28, 2009

SELECT Study Protocol: Headache

Management of Headache – Dose Adjustment

- Dose adjustment for management of lenvatinib toxicity, including headache, was done in accordance with the following instructions:

Treatment-Related Toxicity[a]	Management	Dose adjustment
Grade 1	Treatment was continued	No change
Grade 2 – tolerable[b]	Treatment was continued	No change
Grade 2 – intolerable[b]	**Treatment was interrupted[c]** ➢ until resolved to Grade 0–1 or baseline	**One-level dose reduction**
Grade 3	**Treatment was interrupted[c]** ➢ until resolved to Grade 0-1 or baseline	**One-level dose reduction**

- Dose reductions occurred in succession based on the previous dose level
  - ➢ Once the dose was reduced, it was not increased at a later date

Recommended dose	First dosage reduction to	Second dosage reduction to	Third dosage reduction to	Fourth dosage reduction to
24 mg once daily	20 mg once daily	14 mg once daily	10 mg once daily	Discussed with Sponsor

a. NCI CTCAE, version 4.0.
b. Grade 2 toxicities were determined to be tolerable or intolerable by both the patient and investigator.
c. An interruption of lenvatinib for more than 28 days (due to treatment-related toxicities) required a discussion with the sponsor before treatment was resumed.

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1. Protocol E7080-G000-303; 10 Apr 2012; Page 45.

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Arthralgia/Myalgia

SELECT Study Results and Lenvatinib PI Recommendations: Arthralgia/Myalgia

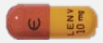
ARTHRALGIA/ MYALGIA[a]	Lenvatinib (n=261)[1]							
	INCIDENCE				ONSET	MANAGEMENT		
						Dose Modifications		Discontinuation
	Grade 1	Grade 2	Grade 3	All Grades	Median Time to First Onset[b]	Lenvatinib Dose Interruption	Lenvatinib Dose Reduction	Lenvatinib
	36%	21%	5%	62%	3.8 weeks	6%	5%	0%

a. This is a post-hoc exploratory analysis for descriptive purpose only; no conclusion can be drawn; b. Median time to first onset in the 162 patients that experienced arthralgia/myalgia.

Lenvatinib PI Recommendations[2]

Severity	Dosage Modifications for Lenvatinib
Grade 2 arthralgia/myalgia that is persistent or intolerable **Grade 3** arthralgia/myalgia	▪ Withhold until improves to Grade 0 to 1 or baseline ▪ Resume at reduced dose

Dose Levels[2] *(Capsules pictured are not actual size)*

Recommended Dose of Lenvatinib		First Dosage Reduction To		Second Dosage Reduction To		Third Dosage Reduction To	
24 mg PO QD	 (two 10-mg capsules + one 4-mg capsule)	**20 mg** PO QD	 (two 10-mg capsules)	**14 mg** PO QD	 (one 10-mg capsule + one 4-mg capsule)	**10 mg** PO QD	 (one 10-mg capsule)

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. *Eisai Stats Report: LEN303MSL-ARMGM: 23 JUL 2020*
2. *Lenvima® [package insert]. Nutley, NJ: Eisai Inc.*

human health care

Grading: Arthralgia/Myalgia

Preferred Terms Included & Related NCI CTCAE v4.0 Terms

Preferred Term *(Listed in alphabetical order)*	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Arthralgia	*Arthralgia*	• *Mild pain*	• *Moderate pain; limiting instrumental ADL*	• *Severe pain; limiting self care ADL*	-	-
Back pain	*Back pain*	• *Mild pain*	• *Moderate pain; limiting instrumental ADL*	• *Severe pain; limiting self care ADL*	-	-
Musculoskeletal pain	*Not listed in CTCAE*	***CTCAE Term or General Guideline used for grading was at the discretion of the investigators***				
Myalgia	*Myalgia*	• *Mild pain*	• *Moderate pain; limiting instrumental ADL*	• *Severe pain; limiting self care ADL*	-	-
Pain in extremity	*Pain in extremity*	• *Mild pain*	• *Moderate pain; limiting instrumental ADL*	• *Severe pain; limiting self care ADL*	-	-

	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	General Guideline	• *Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only intervention not indicated*	• *Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*	• *Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL*	• *Life-threatening consequences; urgent intervention indicated*	• *Death related to AE*

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. NCI CTCAE Version 4.0 Published May 28, 2009.

SELECT Study Protocol: Arthralgia/Myalgia

Management of Arthralgia/Myalgia – Dose Adjustment

- Dose adjustment for management of lenvatinib toxicity, including arthralgia/myalgia, was done in accordance with the following instructions:

Treatment-Related Toxicity[a]	Management	Dose adjustment
Grade 1	Treatment was continued	No change
Grade 2 – tolerable[b]	Treatment was continued	No change
Grade 2 – intolerable[b]	**Treatment was interrupted[c]** ➢ until resolved to Grade 0–1 or baseline	**One-level dose reduction**
Grade 3	**Treatment was interrupted[c]** ➢ until resolved to Grade 0-1 or baseline	**One-level dose reduction**

- Dose reductions occurred in succession based on the previous dose level
  - ➢ Once the dose was reduced, it was not increased at a later date

Recommended dose	First dosage reduction to	Second dosage reduction to	Third dosage reduction to	Fourth dosage reduction to
24 mg once daily	20 mg once daily	14 mg once daily	10 mg once daily	Discussed with Sponsor

a. NCI CTCAE, version 4.0.
b. Grade 2 toxicities were determined to be tolerable or intolerable by both the patient and investigator.
c. An interruption of lenvatinib for more than 28 days (due to treatment-related toxicities) required a discussion with the sponsor before treatment was resumed.

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. Protocol E7080-G000-303; 10 Apr 2012; Page 45.

human health care

Stomatitis

SELECT Study Results and Lenvatinib PI Recommendations: Stomatitis

STOMATITIS[a]	Lenvatinib (n=261)[1]									
	INCIDENCE						ONSET	MANAGEMENT		
								Dose Modifications		Discontinuation
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades	Median Time to First Onset[b]	Lenvatinib Dose Interruption	Lenvatinib Dose Reduction	Lenvatinib
	23%	13%	5%	0%	0%	41%	4.0 weeks	7%	7%	1%

a. This is a post-hoc exploratory analysis for descriptive purpose only; no conclusion can be drawn; b. Median time to first onset in the 107 patients that experienced stomatitis.

Lenvatinib PI Recommendations[2]

Severity	Dosage Modifications for Lenvatinib
Grade 2 stomatitis that is persistent or intolerable **Grade 3** stomatitis	▪ Withhold until improves to Grade 0 to 1 or baseline ▪ Resume at reduced dose
Grade 4 stomatitis	▪ **Permanently discontinue**

Dose Levels[2] *(Capsules pictured are not actual size)*

Recommended Dose of Lenvatinib		First Dosage Reduction To		Second Dosage Reduction To		Third Dosage Reduction To	
24 mg PO QD	 (two 10-mg capsules + one 4-mg capsule)	**20 mg** PO QD	 (two 10-mg capsules)	**14 mg** PO QD	 (one 10-mg capsule + one 4-mg capsule)	**10 mg** PO QD	 (one 10-mg capsule)

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. Eisai Stats Report: LEN303MSL-ARMGM: 23 JUL 2020
2. Lenvima® [package insert]. Nutley, NJ: Eisai Inc.

Grading: Stomatitis

Preferred Terms Included & Related NCI CTCAE v4.0 Terms

Preferred Term *(Listed in alphabetical order)*	CTCAE	
Aphthous stomatitis	*Not listed in CTCAE*	***CTCAE Term or General Guideline used for grading was at the discretion of the investigators***
Glossitis		
Mouth ulceration		
Mucosal inflammation		
Stomatitis		

	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Mucositis oral	• *Asymptomatic or mild symptoms; intervention not indicated*	• *Moderate pain; not interfering with oral intake; modified diet indicated*	• *Severe pain; interfering with oral intake*	• *Life-threatening consequences; urgent intervention indicated*	• *Death*

	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	General Guideline	• *Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only intervention not indicated*	• *Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*	• *Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL*	• *Life-threatening consequences; urgent intervention indicated*	• *Death related to AE*

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. NCI CTCAE Version 4.0 Published May 28, 2009.

SELECT Study Protocol: Stomatitis

Management of Stomatitis – Dose Adjustment

- Dose adjustment for management of lenvatinib toxicity, including stomatitis, was done in accordance with the following instructions:

Treatment-Related Toxicity[a]	Management	Dose adjustment
Grade 1	Treatment was continued	No change
Grade 2 – tolerable[b]	Treatment was continued	No change
Grade 2 – intolerable[b]	**Treatment was interrupted[c]** ➢ until resolved to Grade 0–1 or baseline	**One-level dose reduction**
Grade 3	**Treatment was interrupted[c]** ➢ until resolved to Grade 0-1 or baseline	**One-level dose reduction**
Grade 4	**Lenvatinib was discontinued**	

- Dose reductions occurred in succession based on the previous dose level
  - ➢ Once the dose was reduced, it was not increased at a later date

Recommended dose	First dosage reduction to	Second dosage reduction to	Third dosage reduction to	Fourth dosage reduction to
24 mg once daily	20 mg once daily	14 mg once daily	10 mg once daily	Discussed with Sponsor

a. NCI CTCAE, version 4.0.
b. Grade 2 toxicities were determined to be tolerable or intolerable by both the patient and investigator.
c. An interruption of lenvatinib for more than 28 days (due to treatment-related toxicities) required a discussion with the sponsor before treatment was resumed.

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. Protocol E7080-G000-303; 10 Apr 2012; Page 45.

human health care

Decreased Appetite and Weight

SELECT Study Results and Lenvatinib PI Recommendations: Decreased Appetite and Weight

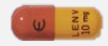
DECREASED APPETITE AND WEIGHT[a]	Lenvatinib (n=261)									
	INCIDENCE						ONSET	MANAGEMENT		
								Dose Modifications		Discontinuation
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades	Median Time to First Onset[b]	Lenvatinib Dose Interruption	Lenvatinib Dose Reduction	Lenvatinib
DECREASED APPETITE	26%	21%	7%	0%	0%	54%	4.2 weeks	13%	10%	0%
DECREASED WEIGHT	10%	28%	13%	N/A	N/A	51%	12.1 weeks	10%	8%	0%

a. This is a post-hoc exploratory analysis for descriptive purpose only; no conclusion can be drawn; b. Median time to first onset in the 142 and 134 patients that experienced decreased appetite and weight, respectively.

Lenvatinib PI Recommendations[2]

Severity	Dosage Modifications for Lenvatinib
Grade 2 decreased appetite and/or decreased weight that is persistent or intolerable	▪ Withhold until improves to Grade 0 to 1 or baseline
Grade 3 decreased appetite and/or decreased weight	▪ Resume at reduced dose
Grade 4 decreased appetite	▪ **Permanently discontinue**

Dose Levels[2] *(Capsules pictured are not actual size)*

Recommended Dose of Lenvatinib		First Dosage Reduction To		Second Dosage Reduction To		Third Dosage Reduction To	
24 mg PO QD	 (two 10-mg capsules + one 4-mg capsule)	**20 mg** PO QD	 (two 10-mg capsules)	**14 mg** PO QD	 (one 10-mg capsule + one 4-mg capsule)	**10 mg** PO QD	 (one 10-mg capsule)

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. *Eisai Stats Report: LEN303MSL-ARRMGM: 23 JUL 2020*
2. *Lenvima® [package insert]. Nutley, NJ: Eisai Inc.*

Grading: Decreased Appetite and Weight

Preferred Terms Included & Related NCI CTCAE v4.0 Terms

Preferred Term *(Listed in alphabetical order)*	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Decreased appetite	*Not listed in CTCAE*	***CTCAE Term or General Guideline used for grading was at the discretion of the investigators***				
Decreased weight						

	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	General Guideline	• *Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only intervention not indicated*	• *Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*	• *Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL*	• *Life-threatening consequences; urgent intervention indicated*	• *Death related to AE*

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. NCI CTCAE Version 4.0 Published May 2009.

SELECT Study Protocol: Decreased Appetite and Weight

Management of Decreased Appetite and Weight – Dose Adjustment

- Dose adjustment for management of lenvatinib toxicity, including decreased appetite and weight, was done in accordance with the following instructions:

Treatment-Related Toxicity[a]	Management	Dose adjustment
Grade 1	Treatment was continued	No change
Grade 2 – tolerable[b]	Treatment was continued	No change
Grade 2 – intolerable[b]	**Treatment was interrupted[c]** ➢ until resolved to Grade 0–1 or baseline	**One-level dose reduction**
Grade 3	**Treatment was interrupted[c]** ➢ until resolved to Grade 0-1 or baseline	**One-level dose reduction**
Grade 4 (for decreased appetite)	**Lenvatinib was discontinued**	

- Dose reductions occurred in succession based on the previous dose level
  - ➢ Once the dose was reduced, it was not increased at a later date

Recommended dose	First dosage reduction to	Second dosage reduction to	Third dosage reduction to	Fourth dosage reduction to
24 mg once daily	20 mg once daily	14 mg once daily	10 mg once daily	Discussed with Sponsor

a. NCI CTCAE, version 4.0.
b. Grade 2 toxicities were determined to be tolerable or intolerable by both the patient and investigator.
c. An interruption of lenvatinib for more than 28 days (due to treatment-related toxicities) required a discussion with the sponsor before treatment was resumed.

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. Protocol E7080-G000-303; 10 Apr 2012; Page 45.

human health care

SELECT Study Results: Decreased Appetite

Concomitant Appetite Stimulants[a,b]

Data cut-off: November 15, 2013

	Lenvatinib (n=261)
Patients who took ≥1 concomitant appetite stimulant	**5.4%**
Megestrol	4.2%
Cyproheptadine	1.1%

a. Analysis of all patients in the full-analysis set; b. Concomitant medications were defined as medications that started before the first dose of study drug and were continuing at the time of the first dose of study drug, or started on or after the date of the first dose of study drug up to 30 days after the patient's last dose. Data should be interpreted with caution as concomitant medications used for a specific AE is not available.

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. CSR E7080-G000-303; 05 Jun 2014; Page 345.

human health care

Palmar-plantar Erythrodysesthesia

SELECT Study Results and Lenvatinib PI Recommendations: Palmar-plantar Erythrodysesthesia

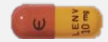
PPE[a]	Lenvatinib (n=261)[1]							
	INCIDENCE				ONSET	MANAGEMENT		
						Dose Modifications		Discontinuation
	Grade 1	Grade 2	Grade 3	All Grades	Median Time to First Onset[b]	Lenvatinib Dose Interruption	Lenvatinib Dose Reduction	Lenvatinib
	16%	13%	3%	32%	5.9 weeks	10%	8%	0%

a. This is a post-hoc exploratory analysis for descriptive purpose only; no conclusion can be drawn; b. Median time to first onset in the 84 patients that experienced PPE.

Lenvatinib PI Recommendations[2]

Severity	Dosage Modifications for Lenvatinib
Grade 2 PPE that is persistent or intolerable **Grade 3** PPE	▪ Withhold until improves to Grade 0 to 1 or baseline ▪ Resume at reduced dose

Dose Levels[2] *(Capsules pictured are not actual size)*

Recommended Dose of Lenvatinib		First Dosage Reduction To		Second Dosage Reduction To		Third Dosage Reduction To	
24 mg PO QD	 (two 10-mg capsules + one 4-mg capsule)	**20 mg** PO QD	 (two 10-mg capsules)	**14 mg** PO QD	 (one 10-mg capsule + one 4-mg capsule)	**10 mg** PO QD	 (one 10-mg capsule)

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. *Eisai Stats Report: LEN303MSL-ARMGM: 23 JUL 2020*
2. *Lenvima® [package insert]. Nutley, NJ: Eisai Inc.*

human health care

Grading: Palmar-plantar Erythrodysesthesia

Preferred Terms Included & Related NCI CTCAE v4.0 Terms

Preferred Term *(Listed in alphabetical order)*	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
PPE syndrome	*PPE syndrome*	• *Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain*	• *Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL*	• *Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL*	-	-

	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	General Guideline	• *Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only intervention not indicated*	• *Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*	• *Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL*	• *Life-threatening consequences; urgent intervention indicated*	• *Death related to AE*

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. NCI CTCAE Version 4.0 Published May 28, 2009

SELECT Study Protocol: Palmar-plantar Erythrodysesthesia

Management of PPE – Dose Adjustment

- Dose adjustment for management of lenvatinib toxicity, including PPE, was done in accordance with the following instructions:

Treatment-Related Toxicity[a]	Management	Dose adjustment
Grade 1	Treatment was continued	No change
Grade 2 – tolerable[b]	Treatment was continued	No change
Grade 2 – intolerable[b]	**Treatment was interrupted[c]** ➢ until resolved to Grade 0–1 or baseline	**One-level dose reduction**
Grade 3	**Treatment was interrupted[c]** ➢ until resolved to Grade 0-1 or baseline	**One-level dose reduction**

- Dose reductions occurred in succession based on the previous dose level
  - ➢ Once the dose was reduced, it was not increased at a later date

Recommended dose	First dosage reduction to	Second dosage reduction to	Third dosage reduction to	Fourth dosage reduction to
24 mg once daily	20 mg once daily	14 mg once daily	10 mg once daily	Discussed with Sponsor

a. NCI CTCAE, version 4.0.
b. Grade 2 toxicities were determined to be tolerable or intolerable by both the patient and investigator.
c. An interruption of lenvatinib for more than 28 days (due to treatment-related toxicities) required a discussion with the sponsor before treatment was resumed.

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. Protocol E7080-G000-303; 10 Apr 2012; Page 45.

human health care

Abdominal Pain

SELECT Study Results and Lenvatinib PI Recommendations: Abdominal Pain

ABDOMINAL PAIN[a]	Lenvatinib (n=261)[1]							
	INCIDENCE				ONSET	MANAGEMENT		
						Dose Modifications		Discontinuation
	Grade 1	Grade 2	Grade 3	All Grades	Median Time to First Onset[b]	Lenvatinib Dose Interruption	Lenvatinib Dose Reduction	Lenvatinib
	18%	12%	2%	31%	6.3 weeks	5%	2%	0%

a. This is a post-hoc exploratory analysis for descriptive purpose only; no conclusion can be drawn; c. Median time to first onset in the 82 patients that experienced abdominal pain.

Lenvatinib PI Recommendations[2]

Severity	Dosage Modifications for Lenvatinib
Grade 2 abdominal pain that is persistent or intolerable **Grade 3** abdominal pain	▪ Withhold until improves to Grade 0 to 1 or baseline ▪ Resume at reduced dose

Dose Levels[2] *(Capsules pictured are not actual size)*

Recommended Dose of Lenvatinib		First Dosage Reduction To		Second Dosage Reduction To		Third Dosage Reduction To	
24 mg PO QD	 (two 10-mg capsules + one 4-mg capsule)	**20 mg** PO QD	 (two 10-mg capsules)	**14 mg** PO QD	 (one 10-mg capsule + one 4-mg capsule)	**10 mg** PO QD	 (one 10-mg capsule)

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. *Eisai Stats Report: LEN303MSL-ARMGM: 23 JUL 2020*
2. *Lenvima® [package insert]. Nutley, NJ: Eisai Inc.*

human health care

Grading: Abdominal Pain

Preferred Terms Included & Related NCI CTCAE v4.0 Terms

Preferred Term *(Listed in alphabetical order)*	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Abdominal discomfort	*Not listed in CTCAE*	***CTCAE Term or General Guideline used for grading was at the discretion of the investigators***				
Abdominal pain	*Abdominal pain*	• *Mild pain*	• *Moderate pain; limiting instrumental ADL*	• *Severe pain; limiting self care ADL*	-	-
Abdominal tenderness	*Not listed in CTCAE*	***CTCAE Term or General Guideline used for grading was at the discretion of the investigators***				
Epigastric discomfort						
Gastrointestinal pain	*Gastrointestinal pain*	• *Mild pain*	• *Moderate pain; limiting instrumental ADL*	• *Severe pain; limiting self care ADL*	-	-
Lower abdominal pain	*Not listed in CTCAE*	***CTCAE Term or General Guideline used for grading was at the discretion of the investigators***				
Upper abdominal pain						

	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	General Guideline	• *Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only intervention not indicated*	• *Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*	• *Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL*	• *Life-threatening consequences; urgent intervention indicated*	• *Death related to AE*

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. NCI CTCAE Version 4.0 Published May 28, 2009.

SELECT Study Protocol: Abdominal Pain

Management of Abdominal Pain – Dose Adjustment

- Dose adjustment for management of lenvatinib toxicity, including abdominal pain, was done in accordance with the following instructions:

Treatment-Related Toxicity[a]	Management	Dose adjustment
Grade 1	Treatment was continued	No change
Grade 2 – tolerable[b]	Treatment was continued	No change
Grade 2 – intolerable[b]	**Treatment was interrupted[c]** ➢ until resolved to Grade 0–1 or baseline	**One-level dose reduction**
Grade 3	**Treatment was interrupted[c]** ➢ until resolved to Grade 0-1 or baseline	**One-level dose reduction**

- Dose reductions occurred in succession based on the previous dose level
  - ➢ Once the dose was reduced, it was not increased at a later date

Recommended dose	First dosage reduction to	Second dosage reduction to	Third dosage reduction to	Fourth dosage reduction to
24 mg once daily	20 mg once daily	14 mg once daily	10 mg once daily	Discussed with Sponsor

a. NCI CTCAE, version 4.0.
b. Grade 2 toxicities were determined to be tolerable or intolerable by both the patient and investigator.
c. An interruption of lenvatinib for more than 28 days (due to treatment-related toxicities) required a discussion with the sponsor before treatment was resumed.

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. Protocol E7080-G000-303; 10 Apr 2012; Page 45.

human health care

Proteinuria

SELECT Study Results and Lenvatinib PI Recommendations: Proteinuria

PROTEINURIA[a]	Lenvatinib (n=261)[1]							
	INCIDENCE				ONSET	MANAGEMENT		
						Dose Modifications		Discontinuation
	Grade 1	Grade 2	Grade 3	All Grades	Median Time to First Onset[b]	Lenvatinib Dose Interruption	Lenvatinib Dose Reduction	Lenvatinib
	6%	17%	11%	34%	7.7 weeks	17%	11%	1%

a. This is a post-hoc exploratory analysis for descriptive purpose only; no conclusion can be drawn; b. Median time to first onset in the 88 patients that experienced proteinuria.

Lenvatinib PI Recommendations[2]

Monitor for proteinuria prior to initiating and periodically during treatment

- **If proteinuria ≥ 2+ on urine dipstick** Obtain a 24-hour urine protein sample → **Withhold lenvatinib** → When proteinuria is **≤ 2 g per 24 hours** → **Resume lenvatinib at reduced dose**
- **Permanently discontinue for nephrotic syndrome**

Nephrotic syndrome: a disorder characterized by symptoms that include severe edema, proteinuria, and hypoalbuminemia; it is indicative of renal dysfunction

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. Eisai Stats Report: LEN303MSL-ARMGM: 23 JUL 2020
2. Lenvima® [package insert]. Nutley, NJ: Eisai Inc.

human health care

Grading: Proteinuria

Preferred Terms Included & Related NCI CTCAE v4.0 Terms

Preferred Term *(Listed in alphabetical order)*	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Proteinuria	*Proteinuria*	• *1+ proteinuria; urinary protein <1.0 g/24 hrs*	• *2+ proteinuria; urinary protein 1.0–3.4 g/24 hrs*	• *Urinary protein ≥3.5 g/24 hrs*	-	-

	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	General Guideline	• *Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only intervention not indicated*	• *Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*	• *Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL*	• *Life-threatening consequences ; urgent intervention indicated*	• *Death related to AE*

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. NCI CTCAE Version 4.0 Published May 28, 2009

human health care

SELECT Study Protocol: Proteinuria

Inclusion Criteria and Proteinuria Monitoring

Inclusion Criteria:

- Patients were not eligible for participation if urine protein ≥1 g/24 hour
- A 24-hour urine collection for protein quantitation was only required if proteinuria on urine dipstick testing was >1+

Proteinuria Monitoring:

- Proteinuria assessments during the Treatment Period were required at:[1,2]

Cycle 1	Cycle 2	For Cycle 3 and Subsequent Cycles	Off-Treatment Visit
▪ Day 15	▪ Day 1 and Day 15	▪ Day 1[a] ***a.*** *Note: For patients with urine dipstick testing of proteinuria ≥2+ assessment was also required every 2 weeks (on Day 15 or more frequently as clinically indicated) until the results were 1+ or negative for 3 consecutive months*	

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. Protocol E7080-G000-303; 10 Apr 2012; Pages 39, 68–72.

human health care

SELECT Study Protocol: Proteinuria

Management of Proteinuria

For any
proteinuria ≥2+
on urine dipstick testing

24-hour urine collection for total protein obtained as soon as possible, within 72 hours

Proteinuria was graded based on 24-hour urine collection according to CTCAE v4.0

If
proteinuria ≥2+ was detected on urine dipstick testing
proteinuria was monitored
every 2 weeks (or more frequently as clinically indicated)
until
proteinuria was 1+ or negative on urine dipstick testing
for 3 consecutive months

Proteinuria
24-hour urine collection

If
Grade 1 or Grade 2

Lenvatinib treatment was continued at the same dose

If
Grade 3

Lenvatinib treatment was interrupted

Proteinuria resolved to
Grade 0–1 or baseline

Lenvatinib administration was restarted at one dose level lower

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. Protocol E7080-G000-303; 10 Apr 2012; Pages 44–45.

SELECT Study Protocol: Proteinuria

Management of Proteinuria: Dose Reductions for Adverse Reactions

- Dose reductions occurred in succession based on the previous dose level

Recommended dose	First dosage reduction to	Second dosage reduction to	Third dosage reduction to	Fourth dosage reduction to
24 mg once daily	20 mg once daily	14 mg once daily	10 mg once daily	Discussed with Sponsor

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. Protocol E7080-G000-303; 10 Apr 2012; Page 45.

human health care

Nausea and Vomiting

SELECT Study Results and Lenvatinib PI Recommendations: Nausea and Vomiting

NAUSEA AND VOMITING[a]	Lenvatinib (n=261)[1]									
	INCIDENCE						ONSET	MANAGEMENT		
								Dose Modifications		Discontinuation
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades	Median Time to First Onset[b]	Lenvatinib Dose Interruption	Lenvatinib Dose Reduction	Lenvatinib
NAUSEA	**27%**	**17%**	**2%**	N/A	N/A	**47%**	**7.8 weeks**	**11%**	**6%**	**0%**
VOMITING	**23%**	**10%**	**2%**	**0%**	**0%**	**36%**	**13.7 weeks**	**6%**	**4%**	**0%**

a. This is a post-hoc exploratory analysis for descriptive purpose only; no conclusion can be drawn; b. Median time to first onset in the 122 and 93 patients that experienced nausea and vomiting, respectively.

Lenvatinib PI Recommendations[2]

Severity	Dosage Modifications for Lenvatinib
Grade 2 nausea and/or vomiting that is persistent or intolerable	▪ Withhold until improves to Grade 0 to 1 or baseline
Grade 3 nausea and/or vomiting	▪ Resume at reduced dose
Grade 4 vomiting	▪ **Permanently discontinue**

Dose Levels[2] *(Capsules pictured are not actual size)*

Recommended Dose of Lenvatinib		First Dosage Reduction To		Second Dosage Reduction To		Third Dosage Reduction To	
24 mg PO QD	 (two 10-mg capsules + one 4-mg capsule)	**20 mg** PO QD	 (two 10-mg capsules)	**14 mg** PO QD	 (one 10-mg capsule + one 4-mg capsule)	**10 mg** PO QD	 (one 10-mg capsule)

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. *Eisai Stats Report: LEN303MSL-ARMGM: 23 JUL 2020*
2. *Lenvima® [package insert]. Nutley, NJ: Eisai Inc.*

human health care

Grading: Nausea and Vomiting

Preferred Terms Included & Related NCI CTCAE v4.0 Terms

Preferred Term *(Listed in alphabetical order)*	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nausea	*Nausea*	• *Loss of appetite without alteration in eating habits*	• *Oral intake decreased without significant weight loss, dehydration or malnutrition*	• *Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated*	-	-
Vomiting	*Vomiting*	• *1–2 episodes (separated by 5 minutes) in 24 hrs*	• *3–5 episodes (separated by 5 minutes) in 24 hrs*	• *≥6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated*	• *Life-threatening consequences; urgent intervention indicated*	• *Death*

	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	General Guideline	• *Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only intervention not indicated*	• *Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*	• *Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL*	• *Life-threatening consequences; urgent intervention indicated*	• *Death related to AE*

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. NCI CTCAE Version 4.0 Published May 28, 2009

SELECT Study Protocol: Nausea and Vomiting

Management of Nausea and Vomiting – Dose Adjustment

- Optimal medical management was initiated for nausea and/or vomiting prior to any study treatment interruption or dose reduction
- Dose adjustment for management of lenvatinib toxicity, including nausea and vomiting, was done in accordance with the following instructions:

Treatment-Related Toxicity[a]	Management	Dose adjustment
Grade 1	Treatment was continued	No change
Grade 2 – tolerable[b]	Treatment was continued	No change
Grade 2 – intolerable[b]	**Treatment was interrupted[c]** ➢ until resolved to Grade 0–1 or baseline	**One-level dose reduction**
Grade 3	**Treatment was interrupted[c]** ➢ until resolved to Grade 0-1 or baseline	**One-level dose reduction**
Grade 4 (for vomiting)	**Lenvatinib was discontinued**	

- Dose reductions occurred in succession based on the previous dose level
  - ➢ Once the dose was reduced, it was not increased at a later date

Recommended dose	First dosage reduction to	Second dosage reduction to	Third dosage reduction to	Fourth dosage reduction to
24 mg once daily	20 mg once daily	14 mg once daily	10 mg once daily	Discussed with Sponsor

a. NCI CTCAE, version 4.0.
b. Grade 2 toxicities were determined to be tolerable or intolerable by both the patient and investigator.
c. An interruption of lenvatinib for more than 28 days (due to treatment-related toxicities) required a discussion with the sponsor before treatment was resumed.

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. Protocol E7080-G000-303; 10 Apr 2012; Page 45.

human health care

Diarrhea

SELECT Study Results and Lenvatinib PI Recommendations: Diarrhea

DIARRHEA[a]	Lenvatinib (n=261)[1]									
	INCIDENCE						ONSET	MANAGEMENT		
								Dose Modifications		Discontinuation
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades	Median Time to First Onset[b]	Lenvatinib Dose Interruption	Lenvatinib Dose Reduction	Lenvatinib
	30%	28%	9%	0%	0%	67%	13.1 weeks	18%	10%	0%

a. This is a post-hoc exploratory analysis for descriptive purpose only; no conclusion can be drawn; b. Median time to first onset in the 176 patients that experienced diarrhea.

Lenvatinib PI Recommendations[2]

- Prompt management should be initiated when lenvatinib treatment-related diarrhea occurs

Severity	Dosage Modifications for Lenvatinib
Grade 2 diarrhea that is persistent or intolerable	▪ Withhold until improves to Grade 0 to 1 or baseline
Grade 3 diarrhea	▪ Resume at reduced dose
Grade 4 diarrhea	▪ **Permanently discontinue**

Dose Levels[2] *(Capsules pictured are not actual size)*

Recommended Dose of Lenvatinib		First Dosage Reduction To		Second Dosage Reduction To		Third Dosage Reduction To	
24 mg PO QD	 (two 10-mg capsules + one 4-mg capsule)	**20 mg** PO QD	 (two 10-mg capsules)	**14 mg** PO QD	 (one 10-mg capsule + one 4-mg capsule)	**10 mg** PO QD	 (one 10-mg capsule)

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. *Eisai Stats Report: LEN303MSL-ARMGM: 23 JUL 2020*
2. *Lenvima® [package insert]. Nutley, NJ: Eisai Inc.*

human health care

Grading: Diarrhea

Preferred Terms Included & Related NCI CTCAE v4.0 Terms

Preferred Term *(Listed in alphabetical order)*	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	*Diarrhea*	• *Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline*	• *Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline*	• *Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL*	• *Life-threatening consequences; urgent intervention indicated*	• *Death*

	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	General Guideline	• *Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only intervention not indicated*	• *Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*	• *Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL*	• *Life-threatening consequences; urgent intervention indicated*	• *Death related to AE*

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. NCI CTCAE Version 4.0 Published May 28, 2009

SELECT Study Protocol: Diarrhea

Management of Diarrhea

- The SELECT protocol required initiation of optimal medical management for diarrhea prior to any study treatment interruption or dose reduction[1]
- Drugs that were not prohibited for concomitant use included:
  - Drugs used to ameliorate symptoms, including antidiarrheal drugs[2]

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. Protocol E7080-G000-303; 10 Apr 2012; Page 45.
2. CSR E7080-G000-303; 05 Jun 2014; Page 47.

SELECT Study Protocol: Diarrhea

Management of Diarrhea – Dose Adjustment

- Dose adjustment for management of lenvatinib toxicity, including diarrhea, was done in accordance with the following instructions:

Treatment-Related Toxicity[a]	Management	Dose adjustment
Grade 1	Treatment was continued	No change
Grade 2 – tolerable[b]	Treatment was continued	No change
Grade 2 – intolerable[b]	**Treatment was interrupted[c]** ➢ until resolved to Grade 0–1 or baseline	**One-level dose reduction**
Grade 3	**Treatment was interrupted[c]** ➢ until resolved to Grade 0-1 or baseline	**One-level dose reduction**
Grade 4	**Lenvatinib was discontinued**	

- Dose reductions occurred in succession based on the previous dose level
  - ➢ Once the dose was reduced, it was not increased at a later date

Recommended dose	First dosage reduction to	Second dosage reduction to	Third dosage reduction to	Fourth dosage reduction to
24 mg once daily	20 mg once daily	14 mg once daily	10 mg once daily	Discussed with Sponsor

a. NCI CTCAE, version 4.0.
b. Grade 2 toxicities were determined to be tolerable or intolerable by both the patient and investigator.
c. An interruption of lenvatinib for more than 28 days (due to treatment-related toxicities) required a discussion with the sponsor before treatment was resumed.

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. Protocol E7080-G000-303; 10 Apr 2012; Page 45.

human health care

SELECT Study Results: Diarrhea

Concomitant Antidiarrheal Medications[a,b,c]

Data cut-off: November 15, 2013

	Lenvatinib (n=261)
Antidiarrheal microorganisms	**13.0%**
Lactobacillus acidophilus	3.4%
Probiotics nos	2.7%
Bifidobacterium bifidum	2.3%
Saccharomyces boulardii	1.5%
Bifidobacterium nos	1.1%
Lactomin	1.1%
Bifidobacterium infantis	0.4%
Bifidobacterium lactis	0.4%
Narimax forte	0.4%
Probiotica P3	0.4%
Other antidiarrheals	**1.9%**
Antipropulsives	**37.9%**
Loperamide	37.2%
Lomotil	3.8%
Papaver somniferum	0.8%

a. Analysis of all patients in the full-analysis set
b. The SELECT study protocol required optimal medical management of diarrhea prior to any lenvatinib dose interruption or dose reduction
c. Concomitant medications were defined as medications that started before the first dose of study drug and were continuing at the time of the first dose of study drug, or started on or after the date of the first dose of study drug up to 30 days after the patient's last dose. Data should be interpreted with caution as concomitant medications used for a specific AE is not available.

Eisai is unable to suggest individualized treatment approaches or provide advice or recommendations outside of the PI for the management of patients taking lenvatinib.

1. CSR E7080-G000-303; 05 Jun 2014; Pages 331, 338 and 351.