CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206947Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA #	NDA 206947
Applicant Name	Eisai Inc.
Date of Submission	August 14, 2014
PDUFA Goal Date	April 14, 2015
Proprietary Name / Established (USAN) Name	Lenvima/ lenvatinib
Dosage Forms / Strength	capsule for oral administration/ 4 mg and 10 mg
Proposed Indication(s)	"for the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer"
Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Division Director	Patricia Keegan
Regulatory Project Manager Review	Deanne Varney
Medical Officer Review	Abhilasha Nair
Statistical Review	Janet (Xiaoping) Jiang
Pharmacology Toxicology Review	Emily Fox
CMC Review	Gaetan Ladouceur and Amit K. Mitra
Biopharmaceutics Review	Okpo Eradiri
Clinical Pharmacology Review	Jun Yan, Anshu Marathe, Ping Zhao, Robert Schuck
QT-IRT Review	Jiang Liu
OPDP	Nick Senior
Patient Labeling Team Review	Nathan Caulk
OSI	Lauren Iacono-Conors
CDTL Review	Steven Lemery
OSE/DMEPA Review	Otto Townsend
OSE/DRISK Review	Carolyn Yancey
DPMH Consult	Miriam Dinatale

OND=Office of New Drugs
CMC=Chemistry, Manufacturing, and Controls
QT-IRT=QT Interdisciplinary Review Team
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
DPMH=Division of Pediatric and Maternal Health

1. Introduction and Background

On August 14, 2014, Eisai submitted NDA 206947 for lenvatinib for the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer (DTC).

Lenvatinib inhibits multiple receptor tyrosine kinases, including VEGFR1 (FLT1), VEGFR2 (KDR), VEGFR3 (FLT4), fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFRα, KIT, and RET.

Available therapies

Radioiodine-refractory differentiated thyroid cancer is a serious and life-threatening disease, with an estimated 10-year survival rate of approximately 10%. There are two drugs approved for this population: doxorubicin and sorafenib.

- Doxorubicin was approved in the mid-1970's for the treatment of nine cancer types, including thyroid cancer. The basis for approval for the treatment of thyroid cancer is objective tumor shrinkage (response rate), with literature at the time of the initial approval citing a 30% response rate (14/46) in patients with advanced refractory, metastatic thyroid carcinoma from single-arm trials. There is no evidence from published literature that doxorubicin improves overall survival (OS) or progression-free survival (PFS).

- Sorafenib received regular approval in 2013 for the treatment of radiation-refractory, progressive, differentiated thyroid cancer, based on the results of randomized, placebo-controlled trial (DECISION) enrolling 471 patients. The trial demonstrated a statistically significant and clinically important improvement in PFS [hazard ratio (HR) 0.59 (95% confidence intervals (CI): 0.45, 0.76); p <0.001, two-sided stratified log-rank test] with median PFS times of 10.8 months in the sorafenib arm and 5.8 months in the placebo arm. The overall response rate, consisting of partial responses, was higher for the sorafenib arm compared with placebo (12.2% vs. 0.5%). The median duration of response was 10.2 months in sorafenib arm and 20 months for the single response observed in the placebo arm.

2. CMC

There are no issues that would preclude approval from a CMC perspective. CMC reviewers have provided an overall acceptability of the manufacturing of the drug product and drug substance. There are no outstanding sterility issues. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months when stored at 25 °C.

Lenvatinib is manufactured as a mesylate salt, (b) (4) and has a very low solubility in aqueous solutions. It will be marked as 4 mg and 10 mg immediate release oral capsules.

3. Nonclinical Pharmacology/Toxicology

There are no issues that would preclude approval from a nonclinical perspective.

In vivo (tumor xenograft) and in vitro studies supporting the anti-angiogenic and tumor growth inhibition of lenvatinib were submitted. In addition, the NDA contained reports of repeat-dose toxicology studies with daily dosing for up to 26 and 39 weeks in rats and monkeys, respectively, safety pharmacology studies, and embryofetal development studies.

Elimination was primarily through the fecal route in animals and humans. Lenvatinib was widely distributed in animal tissues with high levels of the drug observed in the GI tract, liver, kidney, and aorta all target organs identified clinically. The major target organs identified in general toxicology studies conducted in rats, monkeys, and dogs included the gastrointestinal tract, kidney, liver, pancreas, bone marrow, growth plates, teeth, secondary lymphoid organs, adrenal gland, and pituitary.

No significant behavioral or physiological changes were observed following a single dose of lenvatinib in safety pharmacology studies. While transient elevations in blood pressure were noted following a single dose of lenvatinib in monkeys and there was no evidence of effects on cardiac electrophysiology based on ECG monitoring in repeat-dose studies.

In embryofetal development studies conducted in both rats and rabbits, lenvatinib was embrotoxic, fetotoxic, and teratogenic at exposures below that achieved in humans receiving lenvatinib at a dose of 24 mg daily. Lenvatinib was detected in milk from lactating rats treated with the drug at levels approximately two-fold higher than plasma concentrations.

With regard to determination of the duration of contraception, the recommendation in labeling is based on the half-life of the product, and on evidence of fetal harm in the embryofetal development studies resulting in a recommendation to continue contraception for 2 weeks (b) (4) after the last dose of lenvatinib.

4. Clinical Pharmacology

There are no issues that would preclude approval from a clinical pharmacology perspective. Lenvatinib was shown to have rapid absorption with maximal concentrations (Cmax) ranging from 1 to 4 hours after oral administration and a terminal elimination half-life of 28 hours. The bioavailability of lenvatinib was not altered when taken after a high-fat meal as compared to the fasted state, although the median Cmax was prolonged from 2 to 4 hours. Exposure to lenvatinib (Cmax and AUC) increased proportionally over the dose range of 3.2 to 32 mg. In vitro, lenvatinib is predominantly bound to human plasma proteins (98% to 99% bound) and measurement of free lenvatinib is variable, therefore, clinical pharmacology reviewers relied on total lenvatinib concentrations in assessing its PK properties.

Based on popPK analyses, there were no clinically important PK interactions between lenvatinib and body weight, gender, race, age, or tumor type. Although the solubility of lenvatinib is pH-dependent, there were no conclusive effects of gastric pH modifying agents (proton-pump inhibitors, H2 blockers, antacids) on the PK of lenvatinib.

Based on organ impairment studies, increased total lenvatinib exposure (AUC0-inf, total) of 119%, 107%, and 180% was demonstrated for patients with mild, moderate, or severe hepatic impairment, respectively, as compared to those with no impairment.

Although lenvatinib is metabolized by CYP3A (and by aldehyde oxidase as well as non-enzymatic pathways), there was no clinically significant effects of lenvatinib exposure by a strong CYP3A4 inhibitor and dose adjustments of lenvatinib are not required when it is administered in conjunction with inhibitors of CYP3A, P-gp, and BCRP or with inducers of CYP3A and P-gp.

No clinically significant increase in total lenvatinib exposure (AUC0-inf, total) was seen in subjects with severe renal impairment. However, since 90% of the lenvatinib-treated patients in Study 303 in the treatment arm of the registration trial underwent dose reduction and/or dose interruption and patients with severe renal impairment are vulnerable to renal toxicities including renal failure, dose adjustment is recommended in patients with severe renal impairment.

Although there was no evidence of an exposure-response (PFS) relationship in Study 303, this may have been confounded by the fact that 90% of patients receiving lenvatinib underwent a dose modification (dose reduction or dose delay).

Conflicting data on the effects of lenvatinib on cardiac electrophysiology were provided in the thorough QT study evaluating the effect of a single 32 mg dose of lenvatinib on the QT/QTc interval in 52 healthy individuals and the results of serial ECG monitoring in Study 303. The thorough QT study did not demonstrate prolongation of the

QT/QTc interval, whereas prolongation of QTc was documented in 8.8% of lenvatinib-treated patients with Grade ≥3 QTc prolongation in 1.5% of lenvatinib-treated patients.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

This NDA is supported by a multicenter, double-blind, placebo-controlled trial (E7080-G00-303). The trial enrolled 392 patients with locally recurrent or metastatic radioactive iodine-refractory differentiated thyroid cancer and radiographic evidence of disease progression within 12 months prior to randomization. Patients were randomized (2:1) to receive either lenvatinib 24 mg orally per day (n = 261) or matching placebo (n = 131). Patients in the placebo arm were allowed to receive lenvatinib following independent radiologic confirmation of disease progression.

A statistically significant prolongation of PFS as determined by independent radiology review was demonstrated [HR 0.21 (95% CI: 0.16, 0.28); p < 0.001, stratified log-rank test]. Median PFS was 18.3 months in the lenvatinib arm and 3.6 months in the placebo arm. Objective response rates were 65% and 2% in the lenvatinib and placebo arms, respectively. No statistically significant difference in overall survival between the two arms was demonstrated. Upon confirmation of progression, 109 (83%) patients randomly assigned to placebo received open-label lenvatinib.

Efficacy Results for Study 303

	LENVIMA N=261	Placebo N=131
Progression-free Survival[a]		
Number of events (%)	107 (41)	113 (86)
Progressive disease	93 (36)	109 (83)
Death	14 (5)	4 (3)
Median PFS in months (95% CI)	18.3 (15.1, NE)	3.6 (2.2, 3.7)
Hazard ratio (95% CI)[b]	0.21 (0.16, 0.28)	
P-value[c]	<0.001	
Objective Response Rate[a]		
Objective response rate	65%	2%
(95% CI)	(59%, 71%)	(0%, 4%)
Complete response	2%	0%
Partial response	63%	2%
P-value[d]	<0.001	
Overall Survival[e]		
Number of deaths (%)	71 (27)	47 (36)
Median OS in months (95% CI)	NE (22.1, NE)	NE (20.3, NE)
Hazard ratio (95% CI)[b]	0.73 (0.50, 1.07)	
P-value[b]	0.10	

[a] Independent radiologic review

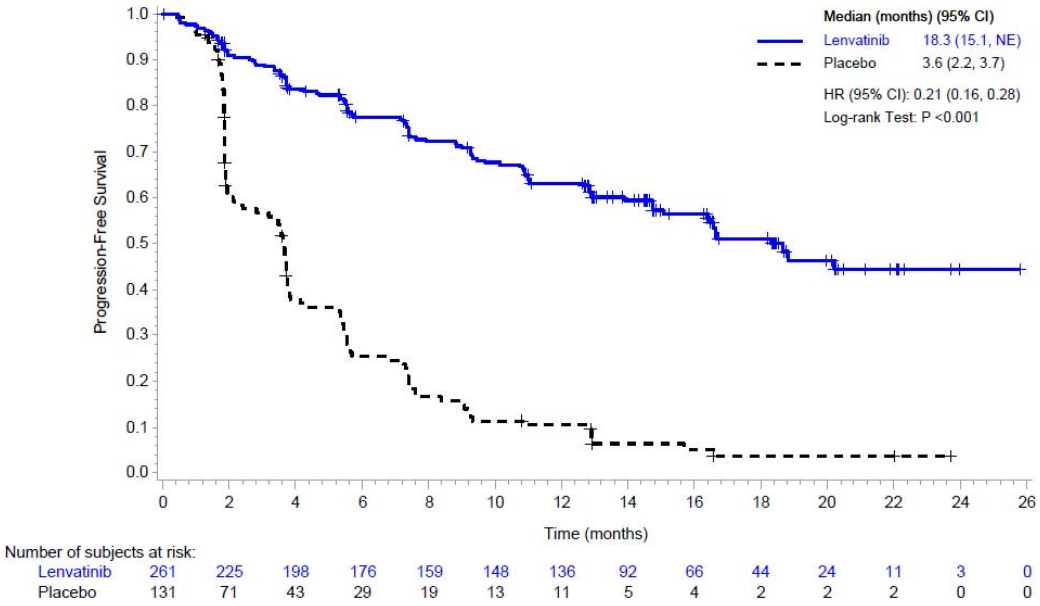
[b] Estimated with Cox proportional hazard model stratified by region (Europe vs North America vs other), age group (≤65 year vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs 1)

[c] Log-rank test stratified by region (Europe vs North America vs other), age group (≤65 years vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs 1)

[d] Cochran-Mantel-Haenszel chi-square test

[e] NE = Not estimable

Progression-Free Survival Curves for Study 303



7. Safety

Safety data obtained in 1108 patients with advanced solid tumors who received LENVIMA as a single agent across multiple clinical studies; the size of the safety database was adequate to identify serious adverse drug reactions occurring at an incidence of 0.3%. The median age was 60 years (range 21-89 years). The dose range was 0.2 mg to 32 mg. The median duration of exposure in the entire population was 5.5 months.

The incidence of common adverse reactions were based on data obtained in Study 303, in which 261 patients with radioactive iodine-refractory differentiated thyroid cancer (RAI-refractory DTC) received at least one dose of lenvatinib and 131 patients received at least on dose of placebo. The median duration of lenvatinib treatment was 16 and the median duration of placebo administration was 3.9 months. The most common adverse reactions of lenvatinib 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%), palmar-plantar erythrodysesthesia (PPE) syndrome (32%), abdominal pain (31%), and dysphonia (31%). The most common serious adverse reactions of lenvatinib were pneumonia (4%), hypertension (3%), and dehydration (3%).

Lenvatinib was poorly tolerated at the starting dose of 24 mg daily, with 68% of patients requiring dose reduction and 18% of patients discontinuing lenvatinib for adverse reactions as compared to 5% requiring dose reduction and 5% discontinuing placebo for adverse reactions. The protocol was amended to lower the lenvatinib dose received by patients from the placebo arm who were allowed to receive lenvatinib following documentation of disease progression to 20 mg orally, once daily.

8. Advisory Committee Meeting

This application was not referred to the Oncologic Drugs Advisory Committee because the safety profile is acceptable for the intended population and there were no controversial issues that would benefit from advisory committee discussion.

9. Pediatrics

Eisai was granted Orphan Drug Designation on December 27, 2012 for lenvatinib for the "treatment of follicular, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer." Therefore, lenvatinib is exempt from Pediatric Research Equity Act (PREA) requirements for the proposed indication.

10. Decision/Action/Risk Benefit Assessment

Regulatory Action: Approval

Risk Benefit Assessment:
A statistically significant prolongation in PFS was demonstrated in LENVIMA-treated patients compared to those receiving placebo [HR 0.21 (0.16, 0.28), p<0.001], with a difference in median PFS of 14.7 months (median PFS 18.3 months for lenvatinib and 2.6 months for placebo). In addition, the objective response rate was significantly higher in the lenvatinib arm (65% vs. 2%, p < 0.001). There were too few events to conduct a formal analysis of survival, however an unplanned interim analysis conducted at FDA's request did not suggest an impairment of survival for patients receiving lenvatinib.

Safety was evaluated in 362 patients receiving at least one dose of study-specific treatment; this included 261 patients who received lenvatinib and 131 who received placebo. Lenvatinib was poorly tolerated at the starting dose of 24 mg daily, with 68% of patients requiring dose reduction and 18% of patients discontinuing lenvatinib for adverse reactions as compared to 5% requiring dose reduction and 5% discontinuing placebo for adverse reactions. The most common adverse reactions resulting in lenvatinib dose reductions were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions resulting in discontinuation of lenvatinib were hypertension (1%) and asthenia (1%).

The risk:benefit assessment is favorable as the adverse reaction profile is similar to that observed with sorafenib, another drug approved for this indication, and medical oncologists are familiar with the identification and management of these adverse reactions. The risk-benefit profile was also assessed by Drs. Keegan, Lemery and Nair. Furthermore, the review team recommends approval of this NDA, and I concur.

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:
No REMS is necessary.

Recommendation for other Postmarketing Requirements and Commitments:
See action letter.

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/s/

TAMY E KIM
02/13/2015

RICHARD PAZDUR
02/13/2015