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Eisai Co., Ltd.

U.S. FDA ACCEPTS FOR PRIORITY REVIEW sNDA FOR EISAI'S ANTICANCER AGENT LENVATINIB SEEKING APPROVAL FOR RENAL CELL CARCINOMA

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that the U.S. Food and Drug Administration (FDA) has accepted for review the supplemental New Drug Application (sNDA) submitted by its U.S. subsidiary Eisai Inc. for Eisai's in-house developed novel anticancer agent lenvatinib mesylate (generic name, "lenvatinib") for use in the treatment of advanced or metastatic renal cell carcinoma, and granted the sNDA Priority Review status.

The FDA's Priority Review designation is assigned to applications for drugs that would, if approved, provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions. Through this process, the FDA has assigned a Prescription Drug User Fee Act (PDUFA) action date (proposed review deadline) of May 16, 2016, 6 months after the sNDA was submitted. Furthermore, lenvatinib has received a Breakthrough Therapy designation from the FDA. In addition, an application seeking approval for use in the treatment of renal cell carcinoma was submitted in Europe in January 2016, and Eisai intends to discuss further steps regarding submission strategies for this potential indication with the regulatory authorities in Japan as well.

This sNDA was based on a Phase II clinical study (Study 205)[1] that compared the safety and efficacy among three groups including a combination of lenvatinib (18 mg) plus everolimus (5 mg), lenvatinib alone (24 mg) and everolimus alone (10 mg) in unresectable advanced or metastatic renal cell carcinoma following one prior vascular endothelial growth factor-targeted therapy. From the results of the study, the group who received the combination of lenvatinib plus everolimus demonstrated a significant extension in progression free survival (PFS), the study's primary endpoint, compared to the everolimus alone group. Additionally, the lenvatinib alone group demonstrated an extension in PFS compared to the everolimus alone group. Both the lenvatinib plus everolimus group and the lenvatinib alone group showed an improvement in objective response rate compared to the everolimus alone group. The most common treatment-emergent adverse events (TEAEs) reported in the lenvatinib plus everolimus group were diarrhea, decreased appetite and fatigue. The most common TEAEs of Grade 3 or higher were diarrhea, hypertension and fatigue.

The number of patients with kidney cancer in the United States is estimated to be approximately 58,000,[2] and renal cell carcinoma comprises more than 90% of all malignancies of the kidney.[3] For advanced or metastatic renal cell carcinoma that is difficult to treat with surgery, the standard treatment is molecular targeted drug therapy, however with low 5-year survival rates, this remains a disease with significant unmet medical need.

Currently lenvatinib has been launched under the brand name Lenvima® in the United States, Japan and Europe for use in the treatment of refractory thyroid cancer*. Eisai is committed to exploring the potential clinical benefits of lenvatinib in order to further contribute to patients with cancer and their families.

*Please refer to the following notes for the approved indications in the United States, Japan and Europe

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[Notes to editors]

1. About lenvatinib mesylate (generic name, "lenvatinib")

Lenvatinib is an orally administered multiple receptor tyrosine kinase (RTK) inhibitor with a novel binding mode that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors (VEGFR1, VEGFR2 and VEGFR3) and fibroblast growth factor (FGF) receptors (FGFR1, FGFR2, FGFR3 and FGFR4) in addition to other proangiogenic and oncogenic pathway-related RTKs (including the platelet-derived growth factor (PDGF) receptor PDGFRα; KIT; and RET) involved in tumor proliferation.

Currently, Eisai has obtained approval for lenvatinib in the United States, Japan, Europe, Korea and Canada as a treatment for refractory thyroid cancer, and is undergoing regulatory review throughout the world including in Asia, Russia, Australia, Brazil and Mexico. More specifically, Eisai has obtained approval for the agent indicated in the United States for treatment for locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer, in Japan for the treatment of unresectable thyroid cancer, and in Europe for the treatment of adult patients with progressive, locally advanced or metastatic differentiated (papillary, follicular, Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine, respectively. Meanwhile, Eisai is conducting a global Phase III study of lenvatinib in hepatocellular carcinoma as well as Phase II studies of lenvatinib in several other tumor types such as endometrial carcinoma and biliary tract cancer.

2. About the Phase II Clinical Study (Study 205)[1]

Study 205 was a multicenter, randomized, open-label study of the combination of lenvatinib (18 mg) plus everolimus (5 mg), lenvatinib alone (24 mg), and everolimus alone (10 mg) in patients with unresectable advanced or metastatic renal cell carcinoma following one prior VEGF-targeted therapy, and was conducted in Europe and the United States. 153 patients were randomized in a 1:1:1 ratio to one of three treatment arms to compare the efficacy and safety of these three regimens.

From the results of the study, the combination of lenvatinib plus everolimus group demonstrated a significant extension in the study's primary endpoint of progression free survival (PFS) compared to the everolimus alone group (median PFS for the lenvatinib plus everolimus group: 14.6 months vs median PFS for the everolimus alone group: 5.5 months; Hazard Ratio (HR) 0.40 [95% CI: 0.24-0.68], p=0.0005). Additionally, median PFS for the lenvatinib alone group was 7.4 months, demonstrating an extension in PFS compared to the everolimus alone group (HR: 0.61 [95% CI: 0.38-0.98]).

The study also assessed objective response rate (ORR) and overall survival (OS) as secondary endpoints. Regarding ORR, both the lenvatinib plus everolimus group and the lenvatinib alone group showed an improvement in ORR compared to the everolimus alone group (lenvatinib plus everolimus: 43%, lenvatinib alone: 27%, everolimus alone: 6%). Furthermore, regarding OS, an updated analysis carried out in December 2014 suggested that lenvatinib plus everolimus extends OS compared to everolimus alone (HR 0.51 [95% CI=0.30-0.88]).

The most common treatment-emergent adverse events (TEAEs) reported in the lenvatinib plus everolimus group were diarrhea, decreased appetite and fatigue. The most common TEAEs of Grade 3 or higher (Common Terminology Criteria for Adverse Events) were diarrhea, hypertension and fatigue.

3. About Renal Cell Carcinoma

The number of patients with renal cancer was estimated to be approximately 338,000 worldwide, including approximately 58,000 in the United States, 115,000 in Europe and 17,000 in Japan.[2] Renal cell carcinoma comprises more than 90% of all malignancies of the kidney,[3] and occurs when malignant cells are found in the lining of the tubules of the kidney. The incidence of renal cell carcinoma in people aged in their late 50s is rising, and is more likely to affect men than women. For advanced or metastatic renal cell carcinoma that is difficult to treat with surgery, the standard treatment method is molecular targeted drug therapy, however with low 5-year survival rates, this remains a disease with significant unmet medical need.

1 Motzer, R, et al. "Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial." *The Lancet Oncology*, 2015; 16, 1473-1482.

2 Globocan 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012, http://globocan.iarc.fr/

3 Eble J.N, ed. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. 3rd ed. *World Health Organization Classification of Tumours*, vol.7 (IARC, 2004)