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Eisai Co., Ltd.

LENVIMA® (LENVATINIB) CAPSULES APPROVED FOR FIRST-LINE TREATMENT OF UNRESECTABLE HEPATOCELLULAR CARCINOMA (HCC) IN SOUTH KOREA

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that its South Korea subsidiary Eisai Korea Inc. received approval for the kinase inhibitor LENVIMA® (lenvatinib mesylate) as a single agent for the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC) from the Ministry of Food and Drug Safety (MFDS) in South Korea. An application seeking approval of LENVIMA for use in the treatment of unresectable HCC was submitted in South Korea in March 2018. This approval for LENVIMA in South Korea marks the second in Asia following approval in Japan. LENVIMA is the first new treatment option approved in ten years as a first-line systemic treatment for HCC in South Korea.
In March 2018, Eisai and Merck & Co., Inc., Kenilworth, N.J., U.S.A, through an affiliate, entered into a strategic collaboration for the worldwide co-development and co-commercialization of LENVIMA. The companies are expected to commence co-commercialization efforts for LENVIMA in South Korea by the end of 2018.

This approval was based on results from REFLECT (Study 304), an open-label, Phase III trial where LENVIMA demonstrated a treatment effect on overall survival (OS)*[1] by statistical confirmation of non-inferiority when compared with the standard of care, sorafenib, in 954 patients with previously untreated unresectable HCC. LENVIMA also demonstrated statistically significant superiority and clinically meaningful improvements in progression-free survival (PFS)*[2] and objective response rate (ORR)*[3].

REFLECT showed that LENVIMA achieved the primary endpoint, demonstrating a treatment effect on OS by statistical confirmation of non-inferiority to sorafenib. Patients treated with LENVIMA experienced a median OS of 13.6 months compared to 12.3 months with sorafenib (Hazard Ratio [HR]: 0.92; 95% Confidence Interval [CI]: 0.79-1.06). The OS analysis was conducted as prespecified in the statistical analysis plan when 351 events had occurred in the LENVIMA arm and 350 events had occurred in the sorafenib arm. Regarding secondary efficacy endpoints, according to independent imaging review based on mRECIST criteria, LENVIMA showed statistically significant superiority and clinically meaningful improvements as compared to sorafenib in median PFS: LENVIMA 7.3 months versus sorafenib 3.6 months (HR: 0.64; 95% CI: 0.55-0.75; $p<0.0001$) and ORR: LENVIMA 40.6% versus sorafenib 12.4% ($p<0.0001$). The five most common adverse reactions observed in patients treated with LENVIMA were hypertension, diarrhea, decreased appetite, weight loss and fatigue, which is consistent with the known side-effect profile of LENVIMA.

Liver cancer is the second leading cause of cancer related deaths and is estimated to be responsible for approximately 750,000 deaths per year globally. Additionally, approximately 780,000 cases are newly diagnosed each year, about 80% of which occur in Asian regions.[1] HCC accounts for 85% to 90% of primary liver cancer cases. Unresectable HCC, for which treatment options are limited, is extremely difficult to treat, and the development of new treatments is necessary.

LENVIMA has been approved as a treatment for refractory thyroid cancer in over 50 countries including the United States, Japan, in Europe and Asia, and as combination with everolimus as a second-line treatment for RCC in over 45 countries including the United States and in Europe.

Since the initial launch, more than 10,000 patients have been treated with LENVIMA, which is approved in more than 50 countries worldwide. In Japan, approximately 3,000 HCC patients have been treated with LENVIMA since the approval of the HCC indication in March 2018.

Eisai positions oncology as a key therapeutic area, and is aiming to discover revolutionary new medicines with the potential to cure cancer. Eisai is committed to exploring the potential clinical benefits of LENVIMA, in collaboration with Merck & Co., Inc., Kenilworth, N.J., U.S.A., as it seeks to contribute further to addressing the diverse needs of, and increasing the benefits provided to cancer patients, their families, and healthcare providers worldwide.

*1 Overall Survival (OS): The time period from the commencement of cancer treatment up until death by any cause. Whether the cause of death is cancer or not is not taken into consideration for this variable.

*2 Progression Free Survival (PFS): PFS is the objectively confirmed time from the commencement of cancer treatment to the date of disease progression, or date of death from any cause, whichever occurs first.

*3 Objective Response Rate (ORR): ORR is the combined proportion of patients whose tumor was eliminated (complete response) and whose tumor was reduced by over 30% in size (partial response) as verified by imaging assessment.

Media Inquiries:
Public Relations Department,
Eisai Co., Ltd.
+81-(0)3-3817-5120

[Notes to editors]

1. About LENVIMA® (lenvatinib mesylate)

Discovered and developed in-house by Eisai, LENVIMA is an orally administered kinase inhibitor with a novel binding mode that selectively inhibits the multi 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 pathway-related RTKs (including the platelet-derived growth factor (PDGF) receptor PDGFRα; KIT; and RET) involved in tumor angiogenesis, tumor progression and modification of tumor immunity.

Currently, Eisai has obtained approval for LENVIMA as a treatment for refractory thyroid cancer in over 50 countries, including the United States, Japan, in Europe and Asia. Additionally, Eisai has obtained approval for the agent in combination with everolimus as a second-line treatment for RCC in over 45 countries, including the United States and in Europe. In Europe, the agent was launched under the brand name Kisplyx® for RCC.

In addition, LENVIMA has been approved as a treatment for hepatocellular carcinoma in Japan, the United States and Europe. Eisai has submitted applications for an indication covering hepatocellular carcinoma in China (October 2017, designated for Priority Review and Approval in December 2017), Taiwan (December 2017), and other countries.

It is important to note that the dose for LENVIMA for patients with unresectable HCC is based on the patient's weight (12 mg for patients weighing 60 kilograms or more, 8 mg for patients weighing less than 60 kilograms); the recommended dosage and dose adjustments are described in the full prescribing information.

2. About the Eisai and Merck & Co., Inc., Kenilworth, N.J., U.S.A. Strategic Collaboration

In March 2018, Eisai and Merck & Co., Inc., Kenilworth, N.J., U.S.A, through an affiliate, entered into a strategic collaboration for the worldwide co-development and co-commercialization of LENVIMA (lenvatinib). Under the agreement, the companies will jointly develop and commercialize LENVIMA, both as monotherapy and in combination with Merck & Co., Inc., Kenilworth, N.J., U.S.A.'s anti-PD-1 therapy KEYTRUDA® (pembrolizumab). In addition to ongoing clinical studies of the combination, the companies will jointly initiate new clinical studies evaluating the LENVIMA and KEYTRUDA combination to support 11 potential indications in six types of cancer, as well as a basket trial targeting six additional cancer types.

3. About the REFLECT Trial (Study 304)

REFLECT was a large (n=954) Phase III, randomized, multicenter, open-label trial conducted by Eisai to compare the efficacy and safety of lenvatinib versus sorafenib as a first-line systemic treatment in patients with unresectable hepatocellular carcinoma (HCC). Patients at 154 trial sites in 20 countries were randomized to receive lenvatinib 12 mg or 8 mg once a day depending on body weight (≥60 kg or <60 kg, respectively) (n=478) or sorafenib 400 mg twice a day (n=476). Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint of this study was overall survival, tested first for non-inferiority to sorafenib, then for superiority. REFLECT showed that LENVIMA achieved the primary endpoint, demonstrating a treatment effect on OS by statistical confirmation of non-inferiority to sorafenib. Patients treated with LENVIMA experienced a median OS of 13.6 months compared to 12.3 months with sorafenib (Hazard Ratio [HR]: 0.92; 95% Confidence Interval [CI]: 0.79-1.06).

In addition, LENVIMA showed statistically significant superiority and clinically meaningful improvements in the secondary efficacy endpoints of PFS and ORR, as confirmed by a blinded independent imaging review (IIR).

Median PFS was doubled with LENVIMA compared to sorafenib: 7.3 months versus 3.6 months (HR: 0.64; 95% CI: 0.55–0.75; p<0.0001) per blinded independent imaging review based on mRECIST criteria, and 7.3 months with LENVIMA versus 3.6 months with sorafenib (HR: 0.65; 95% CI: 0.56–0.77) per RECIST 1.1. LENVIMA showed nearly 3.5 times the ORR of sorafenib: 40.6% (95% CI: 36.2-45.0) (complete response [CR]=2% (n=10), partial response [PR]=38% (n=184)) vs. 12.4% (95% CI: 9.4-15.4) (CR=1% (n=4), PR=12% (n=55)) per blinded independent imaging review based on mRECIST criteria, respectively (p<0.0001), and 18.8% (95% CI: 15.3-22.3) with LENVIMA versus 6.5% (95% CI: 4.3-8.7) with sorafenib per RECIST 1.1.

In addition, median time to progression (TTP) was doubled with LENVIMA compared to sorafenib: 7.4 months versus 3.7 months (HR: 0.60; 95% CI: 0.51-0.71; p<0.0001) per blinded independent imaging review based on mRECIST criteria, and 7.4 months with LENVIMA versus 3.7 months with sorafenib (HR: 0.61; 95% CI: 0.51-0.72; p<0.0001) per RECIST 1.1.

The results of the REFLECT trial were published in *The Lancet* 2018, 391 (10126), 1163-1173 (published online on February 9, 2018).

4. About Unresectable Hepatocellular Carcinoma (HCC)

Liver cancer is the second leading cause of cancer related deaths and is estimated to be responsible for 750,000 deaths per year globally. Additionally, 780,000 cases are newly diagnosed each year. There is a large regional difference, with about 80% of new cases occurring in Asian regions, including China and Japan.[1] HCC accounts for 85% to 90% of primary liver cancer cases. HCC is associated with chronic liver disease, in particular cirrhosis. Major causes of cirrhosis include hepatitis B virus and hepatitis C virus. However, according to a recent investigation, non-B/non-C HCC is on the rise. Surgery is the first option for treatment, but for patients with unresectable HCC who are not amenable for potentially curative therapeutic interventions, which include liver transplant, surgical resection, and tumor ablation (typically radiofrequency ablation or cryotherapy), or who are not suitable for transarterial chemoembolization (TACE), treatment options are limited and the prognosis is very poor.

[1] GLOBOCAN2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. http://globocan.iarc.fr/

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