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Anticancer Agent LENVIMA® Approved for Additional Indication of Unresectable Hepatocellular Carcinoma (HCC) in Japan, First Approval Worldwide for LENVIMA for HCC

First New Front-Line Treatment Option for HCC Approved in Japan in Nearly 10 Years

First Approval under Global Strategic Collaboration between Eisai Co., Ltd. and Merck & Co., Inc., Kenilworth, N.J., U.S.A

TOKYO March 23, 2018 – Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") and Merck & Co., Inc., Kenilworth, N.J., U.S.A. (known as MSD outside the United States and Canada), today announced that the multiple receptor tyrosine kinase inhibitor LENVIMA® (generic name: lenvatinib mesylate) has been approved in Japan for unresectable hepatocellular carcinoma (HCC). This is the first approval worldwide for LENVIMA for the indication of unresectable HCC and the first new systemic therapy to be approved in Japan for the front-line treatment of HCC in approximately 10 years. Additionally, this is the first regulatory approval for LENVIMA under the global strategic collaboration agreement executed in March 2018 between Eisai and Merck & Co., Inc., Kenilworth N.J., U.S.A. for the co-development and co-commercialization of LENVIMA*.

This approval was based on a Phase III clinical study (Study 304 / REFLECT study) conducted by Eisai investigating LENVIMA as a first-line treatment in patients with unresectable HCC.[1] In this study, LENVIMA demonstrated statistically significant non-inferiority of overall survival (OS) (13.6 months) compared to sorafenib (12.3 months) (hazard ratio [HR] 0.92, 95% confidence interval [CI]=0.79-1.06). Additionally, LENVIMA showed highly statistically significant and clinically meaningful improvements as compared to sorafenib in the secondary endpoints of progression free survival (PFS) (HR 0.66, 95% CI=0.57-0.77, p<0.00001), time to progression (TTP) (HR 0.63, 95% CI=0.53-0.73, p<0.00001), and objective response rate (ORR) (LENVIMA 24% versus sorafenib 9%, p<0.00001). Furthermore, LENVIMA helped to delay deterioration in several quality of life (QOL) and symptom domains (pre-specified secondary endpoint) including in areas such as pain and diarrhea, compared to sorafenib (nominal p-value<0.05).

In this study, the five most common adverse events observed in the LENVIMA arm were hypertension (42%), diarrhea (39%), decreased appetite (34%), weight loss (31%) and fatigue (30%), which is consistent with the known safety profile of LENVIMA.

Liver cancer is the second leading cause of cancer related deaths with approximately 750,000 deaths per year estimated globally.[2] Additionally, approximately 780,000 cases are newly diagnosed each year, about 80 percent of which occur in Asia, including Japan and China.[2] HCC accounts as the primary reason for 85 percent to 90 percent of liver cancer cases. It is estimated that there are approximately

42,000 HCC patients in Japan,[3] with approximately 26,000 deaths every year.[4] To-date, treatment options for unresectable HCC have been limited and the prognosis is very poor, emphasizing that this is an area of high unmet medical need.

"With the approval of this additional indication of unresectable HCC for LENVIMA, we are proud to be able to deliver the first new front-line systemic therapy treatment option for HCC in Japan in approximately 10 years, and expect this will contribute to HCC treatment" said Dr. Takashi Owa, Eisai Oncology Business Group Chief Medicine Creation Officer. "Eisai will continue with its efforts in oncology research and development in order to deliver hopes for a potential cure for cancer to patients and their families."

"Today's approval is an important first for LENVIMA and a significant first regulatory event under our collaboration with Eisai," said Dr. Roy Baynes, Senior Vice President and Head of Global Clinical Development, Chief Medical Officer, Merck & Co, Inc. Kenilworth, N.J., U.S.A. "We congratulate Eisai on the approval of this new indication and look forward to working together to bring this important treatment option to patients."

Having received approval of this indication, Eisai will receive a development milestone payment from Merck & Co., Inc., Kenilworth N.J. U.S.A. There are no changes to Eisai's consolidated financial results forecasts for the fiscal year ending March 31, 2018 based on the receipt of this milestone payment.

*Details of the collaboration in Japan are currently under discussion between the two companies.

LENVIMA Product Details in Japan (underlined parts have been added)

1) Product name
   LENVIMA® Capsule 4 mg
2) Generic name
   Lenvatinib mesylate
3) Indication
   Unresectable thyroid cancer, <u>unresectable hepatocellular carcinoma</u>
4) Dosage and Administration
   Unresectable thyroid cancer
   The usual adult dose is 24 mg as lenvatinib administered orally once a day. The dose may be reduced depending on the condition of the individual patient.
   <u>Unresectable hepatocellular carcinoma</u>
   <u>The usual adult dose is an amount of lenvatinib in accordance with body weight administered orally once a day. For adults weighing 60 kg and over, the dose should be 12 mg. For adults weighing less than 60 kg, the dose should be 8 mg. The dose may be reduced depending on the condition of the individual patient.</u>

About LENVIMA (lenvatinib mesylate)

Discovered by Eisai, LENVIMA 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 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, LENVIMA is approved 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 treatment for renal cell carcinoma (second-line) in over 40 countries, including the United States and in Europe. In Europe, the agent was launched under the brand name Kisplyx® for renal cell carcinoma.

Outside of Japan, Eisai has submitted applications for an indication covering hepatocellular carcinoma in the United States and Europe (July 2017), China (October 2017), Taiwan (December 2017) and other countries.

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. entered into a strategic collaboration for the worldwide co-development and co-commercialization of LENVIMA. Under the agreement, the companies will develop and commercialize LENVIMA jointly, 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/KEYTRUDA combination to support 11 potential indications in six types of cancer (endometrial cancer, non-small cell lung cancer, hepatocellular carcinoma, head and neck cancer, bladder cancer and melanoma), as well as a basket trial targeting multiple cancer types.

About the REFLECT Study (Study 304)[1]

The REFLECT study is a multicenter, open-label, randomized, global Phase III study comparing the efficacy and safety of LENVIMA versus sorafenib, a standard treatment for advanced HCC, as a first-line treatment for patients with unresectable HCC. In the study, 954 patients were randomized in a 1:1 ratio to receive LENVIMA 12 mg (≥60 kg) or 8 mg (<60 kg) once a day depending on baseline body weight (n = 478) or sorafenib 400 mg twice a day (n = 476). Treatment was continued until disease progression or unacceptable toxicity.

The primary endpoint of the study was OS, with the goal of demonstrating non-inferiority. Other factors including PFS, TTP, ORR and QOL were assessed as secondary endpoints.

According to the results of the study, LENVIMA met the statistical criteria for non-inferiority in the primary endpoint of median OS (13.6 months) compared to sorafenib (12.3 months) (HR 0.92, 95% [CI] = 0.79-1.06).

Additionally, LENVIMA showed statistically significant improvements in the three secondary efficacy endpoints (investigator assessment), doubling sorafenib's median values and ratios: median PFS (LENVIMA 7.4 months versus sorafenib 3.7 months, [HR 0.66, 95% CI = 0.57-0.77, p<0.00001]), median TTP (LENVIMA 8.9 months versus sorafenib 3.7 months, [HR 0.63, 95% CI = 0.53-0.73, p<0.00001]) and ORR (LENVIMA 24% versus sorafenib 9%, [p<0.00001]).

Furthermore, the European Organisation for Research and Treatment of Cancer's (EORTC) health-related QOL questionnaires QLQ-C30 and QLQ-HCC18 were used for the assessment. In both groups, scores decreased after the administration of the agents. However, within three categories in EORTC QLQ-C30 (role functioning, pain, diarrhea) and two categories in QLQ-HCC18 (nutrition, body image), it was found that LENVIMA helped to delay deterioration of QOL compared to sorafenib (nominal p-value<0.05).

In this study, the five most common adverse events observed in the LENVIMA arm were hypertension (42%), diarrhea (39%), decreased appetite (34%), weight loss (31%) and fatigue (30%), which is consistent with the known safety profile of LENVIMA.

About Eisai Co., Ltd.

Eisai Co., Ltd. is a leading global research and development-based pharmaceutical company headquartered in Japan. We define our corporate mission as "giving first thought to patients and their families and to increasing the benefits health care provides," which we call our *human health care* (*hhc*) philosophy. With approximately 10,000 employees working across our global network of R&D facilities, manufacturing sites and marketing subsidiaries, we strive to realize our *hhc* philosophy by delivering innovative products in various therapeutic areas with high unmet medical needs, including Oncology and Neurology.

As a global pharmaceutical company, our mission extends to patients around the world through our investment and participation in partnership-based initiatives to improve access to medicines in developing and emerging countries.

For more information about Eisai Co., Ltd., please visit www.eisai.com.

[1] M Kudo, et al. "Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial" *The Lancet*, 2018

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

[3] Ministry of Health, Labour and Welfare, 2014 Patient Survey

[4] Ministry of Health, Labour and Welfare, 2014 Population Trends Survey

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