FOR IMMEDIATE RELEASE

EISAI AND MERCK & CO., INC., KENILWORTH, N.J., U.S.A. ANNOUNCE FDA APPROVAL OF LENVIMA® (LENVATINIB) CAPSULES FOR FIRST-LINE TREATMENT OF UNRESECTABLE HEPATOCELLULAR CARCINOMA (HCC)

TOKYO August 17, 2018 – Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") and Merck & Co., Inc., Kenilworth N.J., U.S.A., known as MSD outside of the United States and Canada, announced today that the U.S. Food and Drug Administration (FDA) approved the kinase inhibitor LENVIMA® (lenvatinib mesylate) for the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC). This approval was based on results from REFLECT (Study 304), where LENVIMA demonstrated a proven treatment effect on overall survival (OS) *1 by statistical confirmation of non-inferiority, as well as statistically significant superiority and clinically meaningful improvements in progression-free survival (PFS) *2 and objective response rate (ORR) *3 when compared with sorafenib in patients with previously untreated unresectable HCC. This is the second approval of LENVIMA for use in the treatment of HCC following approval in Japan earlier this year, and the first new systemic therapy to be approved in the U.S. for the first-line treatment of unresectable HCC in approximately 10 years.

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; $p<0.001$) and ORR: LENVIMA 41% versus sorafenib 12% ($p<0.001$).

In the U.S. Package Insert, the most common adverse reactions (≥20%) observed in patients treated with LENVIMA were hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic events, hypothyroidism and nausea. The most common serious adverse reactions (≥2%) reported in patients treated with LENVIMA were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%) and decreased appetite (2%).

The most common adverse reactions (≥20%) observed in patients who received sorafenib were palmar-plantar erythrodysesthesia syndrome, diarrhea, fatigue, hypertension, abdominal pain, decreased appetite, rash, decreased weight and arthralgia/myalgia. The most common serious adverse reactions (≥2%) reported in patients who received sorafenib were ascites (2%) and abdominal pain (2%).

“Unresectable hepatocellular carcinoma is an extremely difficult-to-treat cancer, with no new first-line systemic therapy options for more than a decade,” said Dr. Ghassan Abou-Alfa, medical oncologist, Memorial Sloan Kettering Cancer Center. “REFLECT is the first-ever positive Phase III trial against an active comparator in unresectable HCC. The efficacy and safety data from REFLECT are important findings for oncologists and others in the multidisciplinary teams who treat liver cancer, as well as for our patients who are affected by it.”

Liver cancer is the second leading cause of cancer-related death and is estimated to be responsible for 750,000 deaths per year globally, with 780,000 cases newly diagnosed each year.[1] HCC accounts for 85% to 90% of liver cancer cases. Treatment options for unresectable HCC are limited, and the prognosis is very poor, making this an area of high unmet medical need.

LENVIMA, a kinase inhibitor, was first approved in the U.S. in February 2015 for patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC). In May 2016, LENVIMA was approved in the U.S. in combination with everolimus, for patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy. Under the collaboration, Eisai and Merck & Co., Inc., Kenilworth N.J., U.S.A. initiated co-commercialization activities for LENVIMA in the U.S. in June 2018. Since the initial launch, more than 10,000 patients were 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.

*[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.

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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 to the United States, LENVIMA has been approved as a treatment for hepatocellular carcinoma in Japan as well. Eisai has submitted applications for an indication covering hepatocellular carcinoma in Europe (July 2017), China (October 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 actual 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.

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/KEYTRUDA combination to support 11 potential indications in six types of cancer, as well as a basket trial targeting six additional cancer types.

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. Patients randomized to the LENVIMA arm did not have a statistically significant improvement in OS compared to those in the sorafenib arm. 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<0.001) 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: 41% (95% CI: 36-45%) (complete response (CR)=2.1% (n=10), partial response (PR)=38.5% (n=184)) vs. 12% (95% CI: 10-16%) (CR=0.8% (n=4), PR=11.6% (n=55)) per blinded independent imaging review based on mRECIST criteria, respectively (p<0.001), and 19% (95% CI: 15-22) with LENVIMA versus 7% (95% CI: 4-9) 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).

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.[1] There is a large regional difference, with about 80% of new cases occurring in Asian regions, including China and Japan. Hepatocellular carcinoma accounts for 85% to 90% of primary liver cancer cases. Hepatocellular carcinoma 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 hepatocellular carcinoma is on the rise. Early stage hepatocellular carcinoma is treatable by a wide variety of means, including surgery, radiofrequency ablation, ethanol injection, and chemoembolization therapy, but treatment options for unresectable hepatocellular carcinoma are limited and the prognosis is very poor, meaning that this is an area of high unmet medical need.

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