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Eisai Co., Ltd

ADDITIONAL INDICATION FOR LENVIMA® (LENVATINIB) FOR DIFFERENTIATED THYROID CANCER ACCEPTED IN CHINA

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") has announced that LENVIMA (generic name: lenvatinib), the orally available kinase inhibitor discovered by Eisai, has been accepted by the National Medical Products Administration of China for an application for the additional indication of differentiated thyroid cancer. This application for additional indication marks the second in China following the indication for hepatocellular carcinoma, which was approved in September 2018.

This application was mainly based on the results of the SELECT Study (Study 303)[1] conducted globally for patients with radioactive iodine-refractory differentiated thyroid cancer. In the SELECT study, LENVIMA demonstrated a statistically significant extension in progression-free survival (PFS), which is the primary endpoint, compared to placebo (median PFS in the LENVIMA group: 18.3 months, median PFS in the placebo group: 3.6 months; Hazard Ratio 0.21 [99% CI: 0.14-0.31]; $p<0.001$). Eisai could submit this application earlier by utilizing the results of SELECT study, while local Phase III clinical trial (Study 308) evaluating LENVIMA in patients with radioactive iodine-refractory differentiated thyroid cancer is ongoing in China.

In China, approximately 190,000 new cases of thyroid cancer are diagnosed each year, and approximately 8,600 are likely to die annually.[2] Although treatment is possible for most types of thyroid cancer, there are few treatment options available once thyroid cancer has progressed, therefore it remains a disease with significant unmet medical needs.

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, 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.

* In March 2018, Eisai and Merck & Co., Inc., Kenilworth, N.J., U.S.A. (known as MSD outside the United States and Canada), through an affiliate, entered into a strategic collaboration for the worldwide co-development and co-commercialization of LENVIMA.

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[Notes to editors]

1. About LENVIMA® (lenvatinib mesylate)

LENVIMA, discovered and developed by Eisai, is a kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). LENVIMA inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1-4, the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET. In syngeneic mouse tumor models, lenvatinib decreased tumor-associated macrophages population, increased activated cytotoxic T cells population, and demonstrated greater antitumor activity in combination with an anti-PD-1 monoclonal antibody compared to either treatment alone.

Currently, LENVIMA has been approved as a treatment for thyroid cancer in more than 55 countries including Japan, the United States, and in Europe; as a treatment for hepatocellular carcinoma in more than 50 countries including Japan, the United States, in Europe, China and in Asia; as well as in combination with everolimus as a treatment for renal cell carcinoma (second-line) in more than 50 countries including the United States, in Europe and Asia. Additionally, it is also approved in the combination treatment of LENVIMA plus KEYTRUDA® (pembrolizumab) for advanced endometrial carcinoma in the United States, Australia, and Canada. In Europe, the agent was launched under the brand name Kisplyx® for renal cell carcinoma.

2. About Thyroid Cancer

Thyroid cancer refers to cancer that forms in the tissues of the thyroid gland, located at the base of the throat near the trachea. It is more common in women than in men. The most common types of thyroid cancer, papillary and follicular (including Hürthle cell), are classified as differentiated thyroid cancer and account for approximately 95% of all cases. The remaining cases are classified as either undifferentiated (3-5% of cases) or medullary carcinoma (1-2% of cases). While most differentiated thyroid cancer patients are curable with surgery and radioactive iodine treatment, a small percentage of patients do not respond to therapy.

3. About SELECT Study

The SELECT (Study of E7080 “LEnvatinib” in differentiated Cancer of the Thyroid) study was a multicenter, randomized, double-blind, placebo-controlled Phase III study to compare the progression-free survival (PFS) of patients with radioactive iodine-refractory differentiated thyroid cancer and radiographic evidence of disease progression within the prior 13 months, treated with once-daily, oral LENVIMA (24mg) versus placebo. Patients were randomized 2:1 to either LENVIMA or placebo therapy. The primary endpoint was PFS comparison of both LENVIMA and placebo groups, and the secondary endpoints of the study included response rate (sum of complete and partial responses), overall survival (OS) and safety. The study enrolled 392 patients in over 100 sites in Europe, North and South America and Asia, including Japan, and was conducted by Eisai.

In the study, LENVIMA demonstrated a statistically significant extension in PFS, which is the primary endpoint, compared to placebo (median PFS in the LENVIMA group: 18.3 months, median PFS in the placebo group: 3.6 months; Hazard Ratio 0.21 [99% CI: 0.14-0.31]; $p<0.001$). In addition, the study underlines the rapid response of LENVIMA since the start of administration, with a median time to first objective response of 2.0 months. LENVIMA also demonstrated a statistically significant improvement in response rate compared to placebo ($p<0.001$; LENVIMA: 64.8% vs placebo: 1.5%). In particular, complete response was observed in 1.5% (4 patients) of the LENVIMA group and

zero in the placebo group. The most common LENVIMA treatment-related adverse events of any grade were hypertension, diarrhea, fatigue or asthenia, decreased appetite, weight loss, and nausea.
Currently, a Phase III clinical trial (Study 308) targeting patients with radioactive iodine-refractory differentiated thyroid cancer is ongoing in China.

4. 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., known as MSD outside the United States and Canada, through an affiliate, entered into a strategic collaboration for the worldwide co-development and co-commercialization of LENVIMA. Under the agreement, the companies will jointly develop, manufacture 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.
In addition to ongoing clinical studies evaluating the LENVIMA and KEYTRUDA combination across several different tumor types, the companies will jointly initiate new clinical studies through the LEAP (LEnvatinib And Pembrolizumab) clinical program, which will evaluate the combination to support 11 potential indications in six types of cancer. The LEAP clinical program also includes a basket trial targeting six additional cancer types.

[1] Schlumberger M, et al. Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer. *N. Engl. J. Med.* 2015; 372, 621–630
[2] GLOBOCAN2018: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2018. http://globocan.iarc.fr/