Eisai and Merck Announce European Commission Grants Marketing Authorization for LENVIMA® (lenvatinib) as First-Line Treatment in Adults with Advanced or Unresectable Hepatocellular Carcinoma

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First new, first-line treatment option for advanced or unresectable HCC approved in Europe in a decade

HATFIELD, England & KENILWORTH, N.J.--(BUSINESS WIRE)--Eisai and Merck (NYSE: MRK), known as MSD outside the United States and Canada, announced today that the European Commission (EC) has granted a marketing authorization for the oral receptor tyrosine kinase (RTK) inhibitor LENVIMA® (lenvatinib), as a single agent for the first-line treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy. Treatment options for this type of liver cancer are limited, and the prognosis is poor. LENVIMA is the first new, first-line treatment for advanced or unresectable HCC in a decade to show an overall survival (OS) treatment effect by statistical confirmation of non-inferiority against standard of care.

Liver cancer is the second leading cause of cancer-related deaths and is estimated to be responsible for nearly 750,000 deaths per year globally (69,000 per year in Europe), with over 780,000 cases newly diagnosed each year (71,000 per year in Europe). Hepatocellular carcinoma represents about 90 percent of primary liver cancer cases and due to the underlying nature of the disease, surgery is generally not an option.

“Patients with hepatocellular carcinoma are faced with a cancer that is difficult to treat and has a particularly poor prognosis, with only one systemic first-line treatment option currently available,” said Gary Hendler, Chairman and CEO, Eisai EMEA. “LENVIMA is the first new treatment option to be made available in this first-line systemic treatment setting in over a decade and represents an important new therapeutic option for patients. Eisai and Merck are therefore committed to working together to ensure that patients have rapid access to LENVIMA across Europe.”

“Today’s approval brings an important new first-line treatment option to patients with hepatocellular carcinoma in Europe,” said Dr. Jonathan Cheng, vice president, oncology clinical research, Merck Research Laboratories. “As a result of our efforts with Eisai on LENVIMA, we continue to make significant progress in gaining regulatory approval in countries around the world, as we strive together to make this medicine available to patients in need as quickly as possible.”

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

Currently, LENVIMA is marketed in Japan for the treatment of HCC and in the United States for the treatment of first-line unresectable HCC, and applications seeking approval for this indication have been submitted to additional countries.

About the REFLECT Trial (Study 304)

REFLECT was a large (n=954), Phase 3, randomized, multi-center, open-label trial conducted by Eisai to compare the efficacy and safety of LENVIMA versus sorafenib as a first-line systemic treatment in patients with unresectable HCC. Patients at 154 trial sites in 20 countries were randomized to receive LENVIMA 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 OS, tested first for non-inferiority to sorafenib, then for superiority. The key secondary efficacy endpoints of this study included PFS, time to progression (TTP) and ORR, tested for superiority to sorafenib.

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 (HR: 0.92; 95% 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. Patients randomized to the LENVIMA arm did not have a statistically significant improvement in OS compared to those in the sorafenib arm. 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; p<0.0001) per RECIST 1.1.
- LENVIMA showed nearly 3.5 times the ORR of sorafenib: 41% (95% CI: 36-45%) vs. 12% (95% CI: 9-15%) per blinded independent imaging review based on mRECIST criteria, respectively (p<0.0001), and 19% (95% CI: 15-22%) with LENVIMA versus 7% (95% CI: 4-9%) with sorafenib per RECIST 1.1.
- In REFLECT, the most common adverse events (all grades) observed in ≥30% of patients treated with LENVIMA were hypertension, diarrhea, decreased appetite, fatigue and decreased weight. Fatal adverse events determined by the investigator to be related to LENVIMA treatment occurred in 11 (2%) patients and included hepatic failure (three patients), cerebral hemorrhage (three patients), and respiratory failure (two patients).

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

**About LENVIMA® (lenvatinib) capsules 10 mg and 4 mg**

LENVIMA® (lenvatinib) is a kinase inhibitor that is indicated in the U.S.:

- For the treatment of patients with locally recurrent or metastatic, progressive radioactive iodine-refractory differentiated thyroid cancer (DTC)
- In combination with everolimus, for the treatment of patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy
- For the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC)

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 receptor (FGF) receptors FGFR1-4; the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET. Lenvatinib also exhibited antiproliferative activity in hepatocellular carcinoma cell lines dependent on activated FGFR signaling with a concurrent inhibition of FGF-receptor substrate 2α (FRS2α) phosphorylation.

**Important Safety Information in the U.S.**

**Warnings and Precautions**

**Hypertension.** In DTC, hypertension occurred in 73% of patients on LENVIMA (44% grade 3-4). In RCC, hypertension occurred in 42% of patients on LENVIMA + everolimus (13% grade 3). Systolic blood pressure ≥160 mmHg occurred in 29% of patients, and 21% had diastolic blood pressure ≥100 mmHg. In HCC, hypertension occurred in 45% of LENVIMA-treated patients (24% grade 3). Grade 4 hypertension was not reported in HCC.

Serious complications of poorly controlled hypertension have been reported. Control blood pressure prior to initiation. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at reduced dose when hypertension is controlled or permanently discontinue based on severity.

**Cardiac Dysfunction.** Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, RCC, and HCC, grade 3 or higher cardiac dysfunction occurred in 3% of LENVIMA-treated patients. Monitor for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

**Arterial Thromboembolic Events.** Among patients receiving LENVIMA or LENVIMA + everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in RCC and HCC and 5% in DTC. Grade 3-5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials.

Permanently discontinue following an arterial thrombotic event. The safety of resuming after an arterial thromboembolic event has not been established and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

**Hepatotoxicity.** Across clinical studies enrolling 1,327 LENVIMA-treated patients with malignancies other than HCC, serious hepatic adverse reactions occurred in 1.4% of patients. Fatal events, including hepatic failure, acute hepatitis and hepatorenal syndrome, occurred in 0.5% of patients. In RCC, hepatic encephalopathy occurred in 8% of LENVIMA-treated patients (5% grade 3-5). Grade 3-5 hepatic failure occurred in 3% of LENVIMA-treated patients. 2% of patients discontinued LENVIMA due to hepatic encephalopathy and 1% discontinued due to hepatic failure.

Monitor liver function prior to initiation, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Monitor patients with HCC closely for signs of hepatic failure, including hepatic encephalopathy. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

**Renal Failure or Impairment.** Serious including fatal renal failure or impairment can occur with LENVIMA. Renal impairment was reported in 14% and 7% of LENVIMA-treated patients in DTC and HCC, respectively. Grade 3-5 renal failure or impairment occurred in 3% of patients with DTC and 2% of patients with HCC, including 1 fatal event in each study. In RCC, renal impairment or renal failure was reported in 18% of LENVIMA + everolimus–treated patients (10% grade 3).
Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at reduced dose upon recovery or permanently discontinue for renal failure or impairment based on severity.

**Proteinuria.** In DTC and HCC, proteinuria was reported in 34% and 26% of LENVIMA-treated patients, respectively. Grade 3 proteinuria occurred in 11% and 6% in DTC and HCC, respectively. In RCC, proteinuria occurred in 31% of patients receiving LENVIMA + everolimus (8% grade 3).

Monitor for proteinuria prior to initiation and periodically during treatment. If urine dipstick proteinuria ≥2+ is detected, obtain a 24-hour urine protein. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

**Diabetes.** Of the 737 LENVIMA-treated patients in DTC and HCC, diabetes occurred in 49% (6% grade 3). In RCC, diabetes occurred in 81% of LENVIMA + everolimus–treated patients (19% grade 3). Diabetes was the most frequent cause of dose interruption/reduction, and diabetes recurred despite dose reduction.

Promptly initiate management of diabetes. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

**Fistula Formation and Gastrointestinal Perforation.** Of the 799 patients treated with LENVIMA or LENVIMA + everolimus in DTC, RCC, and HCC, fistula or gastrointestinal perforation occurred in 2%. Fistulas and gastrointestinal perforations have also been reported in other lenvatinib clinical trials and in post-marketing experience. Pneumothorax has been reported with and without clear evidence of a bronchopleural fistula. Some reports of gastrointestinal perforation, fistula, and pneumothorax occurred in association with tumor regression or necrosis. In most cases of fistula formation or gastrointestinal perforation, risk factors such as prior surgery or radiotherapy were present.

Permanently discontinue in patients who develop gastrointestinal perforation of any severity or grade 3-4 fistula.

**QT Interval Prolongation.** In DTC, QT/QTc interval prolongation occurred in 9% of LENVIMA-treated patients and QT interval prolongation of >500 ms occurred in 2%. In RCC, QTc interval increases of >60 ms occurred in 11% of patients receiving LENVIMA + everolimus and QTc interval >500 ms occurred in 6%. In HCC, QTc interval increases of >60 ms occurred in 8% of LENVIMA-treated patients and QTc interval >500 ms occurred in 2%.

Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Withhold and resume at reduced dose upon recovery based on severity.

**Hypocalcemia.** In DTC, grade 3-4 hypocalcemia occurred in 9% of LENVIMA-treated patients. In 65% of cases, hypocalcemia improved or resolved following calcium supplementation with or without dose interruption or dose reduction. In RCC, grade 3-4 hypocalcemia occurred in 6% of LENVIMA + everolimus–treated patients. In HCC, grade 3 hypocalcemia occurred in 0.8% of LENVIMA-treated patients.

Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity and persistence of neurologic symptoms.

**Reversible Posterior Leukoencephalopathy Syndrome.** Across clinical studies of 1,823 patients who received LENVIMA as a single agent, RPLS occurred in 0.3%. Confirm diagnosis of RPLS with MRI. Withhold and resume at reduced dose upon recovery or permanently discontinue for renal failure or impairment based on severity.

**Hemorrhagic Events.** Serious including fatal hemorrhagic events can occur with LENVIMA. In DTC, RCC, and HCC clinical trials, hemorrhagic events, of any grade, occurred in 29% of the 799 patients treated with LENVIMA as a single agent or in combination with everolimus. The most frequently reported hemorrhagic events (all grades and occurring in at least 5% of patients) were epistaxis and hematuria. In DTC, grade 3-5 hemorrhage occurred in 2% of LENVIMA-treated patients, including 1 fatal intracranial hemorrhage among 16 patients who received LENVIMA and had CNS metastases at baseline. In RCC, grade 3-5 hemorrhage occurred in 8% of LENVIMA + everolimus–treated patients, including 1 fatal cerebral hemorrhage. In HCC, grade 3-5 hemorrhage occurred in 5% of LENVIMA-treated patients, including 7 fatal hemorrhagic events.

Serious tumor-related bleeds, including fatal hemorrhagic events, occurred in LENVIMA-treated patients in clinical trials and in the postmarketing setting. In postmarketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than other tumors. Safety and effectiveness of LENVIMA in patients with ATC have not been demonstrated in clinical trials.

Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (e.g., carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

**Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction.** LENVIMA impairs exogenous thyroid suppression. In DTC, 88% of patients had baseline thyroid stimulating hormone (TSH) level ≤0.5 mU/L. In patients with normal TSH at baseline, elevation of TSH level >0.5 mU/L was observed post baseline in 57% of LENVIMA-treated patients. In RCC and HCC, grade 1 or 2 hypothyroidism occurred in 24% of LENVIMA + everolimus–treated patients and 21% of LENVIMA-treated patients, respectively. In patients with normal or low TSH at baseline, elevation of TSH was observed post baseline in 70% of LENVIMA-treated patients in HCC and 60% of LENVIMA + everolimus–treated patients in RCC.

Monitor thyroid function prior to initiation and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

**Wound Healing Complications.** Wound healing complications, including fistula formation and wound dehiscence, can occur with LENVIMA. Withhold for at least 6 days prior to scheduled surgery. Resume after surgery based on clinical judgment of adequate wound healing. Permanently discontinue in patients with wound healing complications.

**Embryo-fetal Toxicity.** Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause...
fetal harm when administered to pregnant women. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended clinical doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. Advise pregnant women of the potential risk to a fetus; and advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 30 days after the last dose.

**Adverse Reactions**

In DTC, the most common adverse reactions (≥30%) observed in LENVIMA-treated patients were hypertension (73%), fatigue (67%), diarrhea (67%), arthralgia/myalgia (62%), decreased appetite (54%), decreased weight (51%), nausea (47%), stomatitis (41%), headache (38%), vomiting (36%), proteinuria (34%), peripheral edema (34%), cough (37%), rash (35%), decreased weight (34%), hemorrhagic events (32%), and proteinuria (31%). The most common serious adverse reactions (≥5%) were renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%). Adverse reactions led to dose reductions or interruption in 89% of patients. The most common adverse reactions (≥5%) resulting in dose reductions were dehydration (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%). Treatment discontinuation due to an adverse reaction occurred in 29% of patients.

In RCC, the most common adverse reactions (≥30%) observed in LENVIMA + everolimus-treated patients were diarrhea (81%), fatigue (73%), arthralgia/myalgia (55%), decreased appetite (53%), vomiting (48%), nausea (45%), stomatitis (44%), hypertension (42%), peripheral edema (42%), cough (37%), abdominal pain (37%), rash (35%), decreased weight (34%), hemorrhagic events (32%), and proteinuria (31%). The most common serious adverse reactions (≥5%) were renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%). Adverse reactions led to dose reductions or interruption in 88% of patients. The most common adverse reactions (≥5%) resulting in dose reductions were fatigue (12%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%). Treatment discontinuation due to an adverse reaction occurred in 20% of patients. The most common adverse reactions (≥1%) resulting in discontinuation of LENVIMA were fatigue (1%), hepatic encephalopathy (2%), hyperbilirubinemia (1%), and hepatic failure (1%).

**Use in Specific Populations**

Because of the potential for serious adverse reactions in breastfed infants, advise women to discontinue breastfeeding during treatment and for at least 1 week after last dose. LENVIMA may impair fertility in males and females of reproductive potential.

No dose adjustment is recommended for patients with mild (CLcr 60–89 mL/min) or moderate (CLcr 30–59 mL/min) renal impairment. LENVIMA concentrations may increase in patients with DTC or RCC and severe (CLcr 15–29 mL/min) renal impairment. Reduce the dose for patients with RCC or DTC and severe renal impairment. There is no recommended dose for patients with HCC and severe renal impairment. LENVIMA has not been studied in patients with end stage renal disease.

No dose adjustment is recommended for patients with HCC and mild hepatic impairment (Child-Pugh A). There is no recommended dose for patients with HCC and moderate hepatic impairment (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

For more information about LENVIMA please see available full Prescribing Information.

**About the Eisai and Merck Strategic Collaboration**

In March 2018, Eisai and Merck, through an affiliate, 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’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. The LENVIMA/KEYTRUDA combination is not approved in any cancer types today.

**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 philosophy. With over 10,000 employees working across our global network of R&D facilities, manufacturing sites and marketing subsidiaries, we strive to realize our human health care philosophy by delivering innovative products in various therapeutic areas with 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.

The development of lenvatinib underscores Eisai’s human health care mission, the company’s commitment to innovative solutions in disease prevention, cure and care for the health and well-being of people worldwide. Eisai is committed to the therapeutic area of oncology and to address the unmet medical needs of patients and their families.

**Merck’s Focus on Cancer**
Our goal is to translate breakthrough science into innovative oncology medicines to help people with cancer worldwide. At Merck, the potential to bring new hope to people with cancer drives our purpose and supporting accessibility to our cancer medicines is our commitment.

As part of our focus on cancer, Merck is committed to exploring the potential of immuno-oncology with one of the largest development programs in the industry across more than 30 tumor types. We also continue to strengthen our portfolio through strategic acquisitions and are prioritizing the development of several promising oncology candidates with the potential to improve the treatment of advanced cancers.

For more information about our oncology clinical trials, visit [www.merck.com/clinicaltrials](http://www.merck.com/clinicaltrials).

**About Merck**

For more than a century, Merck, a leading global biopharmaceutical company known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world’s most challenging diseases. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to advance the prevention and treatment of diseases that threaten people and communities around the world - including cancer, cardio-metabolic diseases, emerging animal diseases, Alzheimer’s disease and infectious diseases including HIV and Ebola. For more information, visit [www.merck.com](http://www.merck.com) and connect with us on Twitter, Facebook, Instagram, YouTube and LinkedIn.

**Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA**

This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the “company”) includes “forward-looking statements” within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company’s management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company’s ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company’s patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company’s 2017 Annual Report on Form 10-K and the company’s other filings with the Securities and Exchange Commission (SEC) available at the SEC’s Internet site ([www.sec.gov](http://www.sec.gov)).

**Language:**

English

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