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FDA Approves LENVIMA® (lenvatinib) Plus KEYTRUDA® (pembrolizumab) Combination for First-Line Treatment of Adult Patients With Advanced Renal Cell Carcinoma (RCC)

LENVIMA Plus KEYTRUDA Is Now Approved for Two Types of Cancer, Including Advanced RCC

Based on Phase 3 CLEAR/KEYNOTE-581 Trial, LENVIMA Plus KEYTRUDA Significantly Reduced Risk of Disease Progression or Death by 61% Versus Sunitinib

TOKYO and KENILWORTH, N.J., Aug. 12, 2021 – Eisai (Headquarters: Tokyo, CEO: Haruo Naito) and Merck & Co., Inc., Kenilworth, N.J., U.S.A. (known as MSD outside the United States and Canada) today announced that the U.S. Food and Drug Administration (FDA) has approved the combination of LENVIMA, the orally available multiple receptor tyrosine kinase inhibitor discovered by Eisai, plus KEYTRUDA, the anti-PD-1 therapy from Merck & Co., Inc., Kenilworth, N.J., U.S.A., for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

The approval is based on results from the pivotal Phase 3 CLEAR (Study 307)/KEYNOTE-581 trial, in which LENVIMA plus KEYTRUDA demonstrated statistically significant improvements versus sunitinib in the efficacy outcome measures of progression-free survival (PFS), overall survival (OS) and confirmed objective response rate (ORR). For PFS, LENVIMA plus KEYTRUDA reduced the risk of disease progression or death by 61% (HR=0.39 [95% CI: 0.32-0.49]; p<0.0001) with a median PFS of 23.9 months versus 9.2 months for sunitinib. For OS, LENVIMA plus KEYTRUDA reduced the risk of death by 34% (HR=0.66 [95% CI: 0.49-0.88]; p=0.0049) versus sunitinib. Additionally, the confirmed ORR was 71% (95% CI: 66-76) (n=252) for patients who received LENVIMA plus KEYTRUDA versus 36% with sunitinib (95% CI: 31-41) (n=129). LENVIMA plus KEYTRUDA achieved a complete response (CR) rate of 16% and partial response (PR) rate of 55% versus a CR rate of 4% and a PR rate of 32% for those who received sunitinib.

Adverse reactions, some of which can be serious or fatal, may occur with LENVIMA, including hypertension, cardiac dysfunction, arterial thromboembolic events, hepatotoxicity, renal failure or impairment, proteinuria, diarrhea, fistula formation and gastrointestinal perforation, QT interval prolongation, hypocalcemia, reversible posterior leukoencephalopathy syndrome, hemorrhagic events, impairment of thyroid stimulating hormone suppression/thyroid dysfunction, impaired wound healing, osteonecrosis of the jaw, and embryo-fetal toxicity. Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should be advised to use effective contraception. Based on the severity of the adverse reaction, LENVIMA should be interrupted, reduced, and/or discontinued. For more information, see "Safety Information" below.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and can affect more than one body system simultaneously. Immune-mediated adverse reactions can occur at any time during or after treatment with KEYTRUDA, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, dermatologic reactions, solid organ transplant rejection, and complications of allogeneic hematopoietic stem cell transplantation. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of KEYTRUDA. Based on the severity of the adverse reaction, KEYTRUDA should be withheld or permanently discontinued and corticosteroids administered if appropriate. KEYTRUDA can also cause severe or life-threatening infusion-related reactions. Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. For more information, see "Safety Information" below.

"This approval is based in part on data demonstrating that LENVIMA plus KEYTRUDA significantly reduced the risk of disease progression or death versus sunitinib," said Dr. Robert Motzer, Jack and Dorothy Byrne Chair in Clinical Oncology, Kidney Cancer Section Head, Genitourinary Oncology Service, Memorial Sloan Kettering Cancer Center. "This is a significant milestone for newly diagnosed patients with advanced renal cell carcinoma and introduces a promising combination option in the first-line setting."

"This FDA approval reinforces the potential of KEYTRUDA plus LENVIMA, which is now approved for two different types of cancer. In the study, KEYTRUDA plus LENVIMA demonstrated a survival benefit for patients with advanced renal cell carcinoma, supporting the importance of this combination as a new first-line treatment option for these patients," said Dr. Gregory Lubiniecki, Vice President, Oncology Clinical Research, Merck & Co., Inc., Kenilworth, N.J., U.S.A. Research Laboratories. "At Merck & Co., Inc., Kenilworth, N.J., U.S.A., we are focused on delivering meaningful innovations that extend the lives of people with cancer. We are proud to

see how our collaboration with Eisai can now help to improve survival outcomes for patients with advanced renal cell carcinoma and are committed to further exploring KEYTRUDA plus LENVIMA in other difficult-to-treat cancers."

"This FDA approval is truly significant for the advanced renal cell carcinoma community. The CLEAR/KEYNOTE-581 trial shows treatment with LENVIMA plus KEYTRUDA resulted in superior outcomes across progression-free survival, overall survival and objective response rate versus sunitinib in patients with advanced renal cell carcinoma," said Dr. Takashi Owa, Chief Medicine Creation and Chief Discovery Officer, Oncology Business Group at Eisai. "This milestone is a testament to our dedication to developing new therapeutic options for people living with advanced cancers, which is fueled by our passion for aiming to improve cancer care for patients, and amplified by the teamwork resulting from our collaboration with Merck & Co., Inc., Kenilworth, N.J., U.S.A."

This approval was reviewed under the FDA's Real-Time Oncology Review (RTOR) pilot program, which aims to improve the efficiency of the review process for applications to ensure that treatments are available to patients as early as possible.

Dr. Motzer has provided consulting and advisory services for Eisai and Merck & Co., Inc., Kenilworth, N.J., U.S.A.

Data Supporting the Approval

The approval was based on data from the CLEAR(Study 307)/KEYNOTE-581 trial (ClinicalTrials.gov, NCT02811861), a Phase 3, multicenter, open-label, randomized trial conducted in 1,069 patients with advanced RCC in the first-line setting. Patients were enrolled regardless of PD-L1 tumor expression status. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomization was stratified by geographic region (North America and Western Europe vs. "Rest of the World") and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups (favorable vs. intermediate vs. poor risk).

Patients were randomized (1:1:1) to one of the following treatment arms:

- LENVIMA (20 mg orally once daily) in combination with KEYTRUDA (200 mg intravenously [IV] every three weeks for up to 24 months); or
- LENVIMA (18 mg orally once daily) in combination with everolimus (5 mg orally once daily); or

- Sunitinib (50 mg orally once daily for four weeks on treatment, followed by two weeks off treatment).

Treatment continued until unacceptable toxicity or disease progression. Administration of LENVIMA plus KEYTRUDA was permitted beyond Response Evaluation Criteria in Solid Tumors (RECIST)-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. KEYTRUDA was continued for a maximum of 24 months; however, treatment with LENVIMA could be continued beyond 24 months. Assessment of tumor status was performed at baseline and then every eight weeks.

The study population characteristics were: median age of 62 years (range: 29 to 88 years), 42% age 65 or older; 75% male; 74% White, 21% Asian, 1% Black, and 2% other races; 18% and 82% of patients had a baseline Karnofsky Performance Status (KPS) of 70 to 80 and 90 to 100, respectively; patient distribution by MSKCC risk categories was 27% favorable, 64% intermediate, and 9% poor. Common sites of metastases in patients were lung (68%), lymph node (45%), and bone (25%).

The major efficacy outcome measures were PFS, as assessed by independent radiologic review (IRC) according to RECIST v1.1, and OS. Additional efficacy outcome measures included confirmed ORR as assessed by IRC. LENVIMA in combination with KEYTRUDA demonstrated statistically significant improvements in PFS, OS, and ORR compared with sunitinib. Efficacy results showed:

Endpoint	**LENVIMA 20mg and KEYTRUDA 200mg every 3 weeks n=355**	**Sunitinib n=357**
Progression-Free Survival (PFS)		
Number of events, n (%)	160 (45%)	205 (57%)
Progressive disease	145 (41%)	196 (55%)
Death	15 (4%)	9 (3%)
Median PFS in months (95% CI)	23.9 (20.8, 27.7)	9.2 (6.0, 11.0)
Hazard ratio* (95% CI)	0.39 (0.32, 0.49)	
p-Value†	<0.0001	
Overall Survival (OS)		
Number of deaths, n (%)	80 (23%)	101 (28%)
Median OS in months (95% CI)	NR (33.6, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.66 (0.49, 0.88)	
p-Value†	0.0049	
Objective Response Rate (Confirmed)		
ORR, n (%)	252 (71%)	129 (36%)
(95% CI)	(66, 76)	(31, 41)
Complete response rate	16%	4%
Partial response rate	55%	32%

p-Value‡	<0.0001
Tumor assessments were based on RECIST 1.1; only confirmed responses are included for ORR. Data cutoff date = 28 Aug 2020 CI = Confidence interval; NE= Not estimable; NR= Not reached *Hazard ratio is based on a Cox Proportional Hazards Model. Stratified by geographic region and MSKCC prognostic groups. †Two-sided p-value based on stratified log-rank test. ‡Two-sided p-value based upon CMH test.	

The median duration of exposure to the combination therapy of LENVIMA and KEYTRUDA was 17 months (range: 0.1 to 39 months).

Fatal adverse reactions occurred in 4.3% of patients who received LENVIMA in combination with KEYTRUDA, including cardio-respiratory arrest (0.9%), sepsis (0.9%), and one case (0.3%) each of arrhythmia, autoimmune hepatitis, dyspnea, hypertensive crisis, increased blood creatinine, multiple organ dysfunction syndrome, myasthenic syndrome, myocarditis, nephritis, pneumonitis, ruptured aneurysm, and subarachnoid hemorrhage.

Serious adverse reactions occurred in 51% of patients receiving LENVIMA plus KEYTRUDA. Serious adverse reactions in ≥2% of patients were hemorrhagic events (5%), diarrhea (4%), hypertension (3%), myocardial infarction (3%), pneumonitis (3%), vomiting (3%), acute kidney injury (2%), adrenal insufficiency (2%), dyspnea (2%), and pneumonia (2%).

Permanent discontinuation of either LENVIMA, KEYTRUDA, or both due to an adverse reaction occurred in 37% of patients receiving LENVIMA in combination with KEYTRUDA; 26% LENVIMA only, 29% KEYTRUDA only and 13% both treatments. The most common adverse reactions (≥2%) resulting in permanent discontinuation of LENVIMA, KEYTRUDA, or the combination were pneumonitis (3%), myocardial infarction (3%), hepatotoxicity (3%), acute kidney injury (3%), rash (3%), and diarrhea (2%).

Dose interruptions of LENVIMA, KEYTRUDA, or both due to an adverse reaction occurred in 78% of patients receiving LENVIMA in combination with KEYTRUDA. LENVIMA was interrupted in 73% of patients, KEYTRUDA was interrupted in 55% of patients, and both treatments were interrupted in 39% of patients. LENVIMA was dose reduced in 69% of patients. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of LENVIMA were diarrhea (26%), fatigue (18%), hypertension (17%), proteinuria (13%), decreased appetite (12%), palmar-plantar erythrodysesthesia syndrome (PPE) (11%), nausea (9%), stomatitis (9%), musculoskeletal pain (8%), rash (8%), increased lipase (7%), abdominal pain (6%), and vomiting (6%), increased alanine aminotransferase (ALT) (5%), and increased amylase (5%). The most common adverse reactions (≥3%) resulting in interruption of KEYTRUDA were

diarrhea (10%), hepatotoxicity (8%), fatigue (7%), lipase increased (5%), amylase increased (4%), musculoskeletal pain (3%), hypertension (3%), rash (3%), acute kidney injury (3%), and decreased appetite (3%). Fifteen percent (15%) of patients treated with LENVIMA in combination with KEYTRUDA received an oral prednisone equivalent to ≥40 mg daily for an immune-mediated adverse reaction. Grade 3 and 4 increased ALT or increased aspartate aminotransferase (AST) was seen in 9% of patients. Grade ≥2 increased ALT or AST was reported in 64 (18%) patients, of whom 20 (31%) received ≥40 mg daily oral prednisone equivalent. Recurrence of Grade ≥2 increased ALT or AST was observed in three patients on rechallenge in patients receiving LENVIMA and 10 patients receiving both LENVIMA and KEYTRUDA.

The most common adverse reactions (All Grades ≥20%) for LENVIMA plus KEYTRUDA were fatigue (63%), diarrhea (62%), musculoskeletal disorders (58%), hypothyroidism (57%), hypertension (56%), stomatitis (43%), decreased appetite (41%), rash (37%), nausea (36%), weight loss, dysphonia and proteinuria (30% each), PPE syndrome (29%), hemorrhagic events and abdominal pain (27% each), vomiting (26%), constipation and hepatotoxicity (25% each), headache (23%), and acute kidney injury (21%). The most common adverse reactions (Grades 3-4) for LENVIMA plus KEYTRUDA were hypertension (29%), diarrhea (10%), fatigue and hepatotoxicity (9% each), weight loss and proteinuria (8% each), acute kidney injury, hemorrhagic events and rash (5% each), musculoskeletal disorders, decreased appetite and PPE (4% each), nausea and vomiting (3% each), stomatitis and abdominal pain (2% each), and constipation, hypothyroidism and headache (1% each).

Clinically relevant adverse reaction (<20%) that occurred in patients receiving LENVIMA plus KEYTRUDA were myocardial infarction (3%) and angina pectoris (1%).

About Renal Cell Carcinoma (RCC)[1,2,3,4,5,6]

Worldwide, it is estimated there were more than 431,000 new cases of kidney cancer diagnosed and more than 179,000 deaths from the disease in 2020. In Japan, there were more than 25,000 new cases and 8,000 deaths in 2020. In the U.S. alone, it is estimated there will be approximately 76,000 new cases of kidney cancer diagnosed and almost 14,000 deaths from the disease in 2021. Renal cell carcinoma is by far the most common type of kidney cancer; about nine out of 10 kidney cancer diagnoses are RCC. Renal cell carcinoma is about twice as common in men as in women. Most cases of RCC are discovered incidentally during imaging tests for other abdominal diseases. Approximately 30% of patients with RCC will have metastatic disease at diagnosis. Survival is highly dependent on the stage at diagnosis, and the five-year survival rate is 13% for patients diagnosed with metastatic disease.

About LENVIMA® (lenvatinib); available as 10mg and 4mg capsules

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. The combination of LENVIMA and everolimus showed increased anti-angiogenic and anti-tumor activity as demonstrated by decreased human endothelial cell proliferation, tube formation, and VEGF signaling in vitro and tumor volume in mouse xenograft models of human renal cell cancer greater than each drug alone. In syngeneic mouse tumor models, lenvatinib decreased tumor-associated macrophages, increased activated cytotoxic T cells, and demonstrated greater antitumor activity in combination with an anti-PD-1 monoclonal antibody compared to either treatment alone.

Currently, LENVIMA has been approved for monotherapy as a treatment for thyroid cancer in over 75 countries including Japan, in Europe, China and in Asia, and in the United States for locally recurrent or metastatic, progressive, radioiodine-refractory differentiated thyroid cancer. In addition, LENVIMA has been approved for monotherapy as a treatment for unresectable hepatocellular carcinoma in over 70 countries including Japan, in Europe, China and in Asia, and in the United States for first-line unresectable hepatocellular carcinoma. LENVIMA has been approved for monotherapy as a treatment for unresectable thymic carcinoma in Japan. It is also approved in combination with everolimus as a treatment for renal cell carcinoma following prior antiangiogenic therapy in over 60 countries, including in Europe and Asia, and in the United States the treatment of adult patients with advanced renal cell carcinoma following one prior anti-angiogenic therapy. In Europe, the agent was launched under the brand name Kisplyx® for renal cell carcinoma. LENVIMA is approved in combination with KEYTRUDA (generic name: pembrolizumab), for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC) in United States. LENVIMA has been approved in combination with KEYTRUDA (generic name: pembrolizumab) as a treatment for advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation in the United States, and has been approved for the similar indication (including conditional approval) in over 10 countries such as Canada and Australia. In some

regions, continued approval for this indication is contingent upon verification and description of clinical benefit in the confirmatory trials.

About KEYTRUDA® (pembrolizumab) Injection, 100mg

KEYTRUDA is an anti-programmed death receptor-1 (PD-1) therapy that works by increasing the ability of the body's immune system to help detect and fight tumor cells. KEYTRUDA is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes which may affect both tumor cells and healthy cells.

Merck & Co., Inc., Kenilworth, N.J., U.S.A. has the industry's largest immuno-oncology clinical research program. There are currently more than 1,500 trials studying KEYTRUDA across a wide variety of cancers and treatment settings. The KEYTRUDA clinical program seeks to understand the role of KEYTRUDA across cancers and the factors that may predict a patient's likelihood of benefitting from treatment with KEYTRUDA, including exploring several different biomarkers.

Safety Information

For safety information on LENVIMA and KEYTRUDA in the United States, please see the LENVIMA Prescribing Information (https://us.eisai.com/-/media/Files/USEisai/792710051-2021-08-11), and visit the KEYTRUDA product website (https://www.keytruda.com).

About the Merck & Co., Inc., Kenilworth, N.J., U.S.A. and Eisai 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 KEYTRUDA, the anti-PD-1 therapy from Merck & Co., Inc., Kenilworth, N.J., U.S.A.

In addition to ongoing clinical studies evaluating the LENVIMA plus KEYTRUDA combination across several different tumor types, the companies have jointly initiated new clinical studies through the LEAP (LEnvatinib And Pembrolizumab) clinical program and are evaluating the combination in 13 different tumor types across more than 20 clinical trials.

Eisai's Focus on Cancer

Eisai focuses on the development of anticancer drugs, targeting the tumor microenvironment (with experience and knowledge from existing in-house discovered compounds) and the driver gene mutation and aberrant splicing (leveraging RNA Splicing Platform) as areas (*Ricchi*) where real patient needs are still unmet, and where Eisai can aim to become a frontrunner in oncology. Eisai aspires to discover innovative new drugs with new targets and mechanisms of action from these *Ricchi*, with the aim of contributing to the cure of cancers.

About Eisai

Eisai is a leading global research and development-based pharmaceutical company headquartered in Japan, with approximately 10,000 employees worldwide. 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. We strive to realize our *hhc* philosophy by delivering innovative products in therapeutic areas with high unmet medical needs, including Oncology and Neurology. In the spirit of *hhc*, we take that commitment even further by applying our scientific expertise, clinical capabilities and patient insights to discover and develop innovative solutions that help address society's toughest unmet needs, including neglected tropical diseases and the Sustainable Development Goals.

For more information about Eisai, please visit www.eisai.com (for global headquarters: Eisai. Co., Ltd.), us.eisai.com (for U.S. headquarters: Eisai, Inc.) or www.eisai.eu (for Europe, Middle East, Africa, Russia, Australia and New Zealand headquarters: Eisai Europe Ltd.), and connect with us on Twitter (U.S. and global) and LinkedIn (for U.S. and EMEA).

Merck & Co., Inc., Kenilworth, N.J., U.S.A.'s Focus on Cancer

Our goal is to translate breakthrough science into innovative oncology medicines to help people with cancer worldwide. At Merck & Co., Inc., Kenilworth, N.J., U.S.A., 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 & Co., Inc., Kenilworth, N.J., U.S.A. 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.

About Merck & Co., Inc., Kenilworth, N.J., U.S.A.

For 130 years, Merck & Co., Inc., Kenilworth, N.J., U.S.A., 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 in pursuit of our mission to save and improve lives. We demonstrate our commitment to patients and population health by increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck & Co., Inc., Kenilworth, N.J., U.S.A. continues to be at the forefront of research to prevent and treat diseases that threaten people and animals – including cancer, infectious diseases such as HIV and Ebola, and emerging animal diseases – as we aspire to be the premier research-intensive biopharmaceutical company in the world. For more information, visit 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 the global outbreak of novel coronavirus disease (COVID-19); 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 2020 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).

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