NEWS RELEASE

Merck Receives Positive EU CHMP Opinion for WELIREG® (belzutifan) in Combination With Lenvatinib for Adults With Advanced Renal Cell Carcinoma With a Clear Cell Component (ccRCC) Following Treatment With an Anti-PD-1/PD-L1 Therapy

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Opinion granted based on positive progression-free survival results from the Phase 3 LITESPARK-011 trial

If approved, this regimen will be the first and only approved combination of a HIF-2α inhibitor and a multi-targeted VEGFR-TKI in the European Union

RAHWAY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today announced the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending approval of WELIREG® (belzutifan), Merck's first-in-class oral hypoxia-inducible factor-2 alpha (HIF-2α) inhibitor, plus lenvatinib, the orally available multiple receptor tyrosine kinase inhibitor (TKI) discovered by Eisai, for the treatment of adult patients with advanced renal cell carcinoma with a clear cell component (ccRCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor. This recommendation will now be reviewed by the European Commission (EC) for marketing authorization in the European Union (EU), Iceland, Liechtenstein and Norway. A final decision is expected in the next two months.

“Patients with advanced renal cell carcinoma in the European Union have limited treatment options if their disease progresses following anti-PD-1 or anti-PD-L1 therapy,” said Dr. Christina Derleth, vice president, global oncology clinical development, Merck Research Laboratories. “This positive opinion is a meaningful step toward potentially bringing this first-of-its-kind regimen to patients in need in the European Union and underscores the important role of WELIREG plus lenvatinib as a new option in the treatment of renal cell carcinoma.”

The recommendation is based on results from the Phase 3 LITESPARK-011 trial. In the study, WELIREG in combination with lenvatinib demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS), one of the study’s dual primary endpoints, reducing the risk of disease progression or death by 26% (HR=0.74 [95% CI, 0.61-0.89]; p=0.001) in patients with advanced ccRCC whose disease progressed on or after treatment with a PD-1 or PD-L1 inhibitor compared to cabozantinib. Initial results for the trial **were presented** at the 2026 American Society of Clinical Oncology (ASCO) Genitourinary (GU) Cancers Symposium. At the final analysis, overall survival (OS), the study’s other dual primary endpoint, did not meet statistical significance for patients who received WELIREG in combination with lenvatinib compared to cabozantinib. WELIREG in combination with lenvatinib reduced the risk of death by 15% (HR=0.85 [95% CI, 0.70-1.03]) in these patients compared to cabozantinib. Additionally, at the final analysis, the combination showed a continued benefit in objective response rate (ORR), a key secondary endpoint, of 53.1% for WELIREG plus lenvatinib versus 40.2% for cabozantinib. Similarly, WELIREG in combination with lenvatinib improved duration of response (DOR), another secondary endpoint, compared to cabozantinib, with a median DOR of 22.0 months versus 11.9 months, respectively. These results were presented at the European Society for Medical Oncology (ESMO) Congress 2026.

In **September 2026**, WELIREG in combination with LENVIMA® (lenvatinib) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult patients with advanced ccRCC following a PD-1 or PD-L1 inhibitor, based on results from the Phase 3 LITESPARK-011 trial.

About LITESPARK-011

LITESPARK-011 is a randomized, open-label Phase 3 trial (ClinicalTrials.gov, **NCT04586231**) evaluating WELIREG in combination with LENVIMA compared to cabozantinib for the treatment of patients with advanced ccRCC. Eligible patients include participants with locally advanced or metastatic ccRCC who have progressed on or after a PD-1 or PD-L1 inhibitor, or within 6 months of completing adjuvant therapy with a PD-1 inhibitor. The trial enrolled 747 patients who were randomized to receive WELIREG (120 mg orally once daily) plus LENVIMA (20 mg orally once daily) or cabozantinib (60 mg orally once daily). The major efficacy endpoints were PFS per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as assessed by blinded independent central review (BICR) and OS. Objective response rate per RECIST v1.1 as assessed by BICR, DOR per RECIST v1.1 as assessed by BICR and safety were additional endpoints.

About renal cell carcinoma

Renal cell carcinoma is the most common type of kidney cancer, with about nine out of 10 kidney cancer diagnoses being RCC. In 2024, there were an estimated 442,570 new cases of kidney cancer and 144,871 deaths from the disease worldwide. Renal cell carcinoma is about twice as common in men as in women. Cases of RCC might be discovered incidentally during imaging tests for other reasons. Approximately 32% of patients with kidney cancer are diagnosed at a regional or metastatic stage. Clear cell renal cell carcinoma, which accounts for about 70% of RCC diagnoses, is the most common subtype.

About Merck's research in genitourinary cancers

Merck is advancing research aimed at helping transform the treatment landscape and broaden options for people with genitourinary (GU) cancers, including bladder, kidney and prostate cancers. Globally, GU cancers account for an estimated 2.6 million new cancer diagnoses each year, equaling over 1 in 8 of all cancer incidences. Through a robust clinical development program with more than 50 ongoing clinical trials evaluating more than 22,000 patients around the world, Merck is investigating the potential of several portfolio medicines and pipeline assets, leveraging multiple novel combination strategies, across various stages of disease, to help address unmet needs in GU cancers.

About WELIREG® (belzutifan) 40 mg tablets, for oral use

WELIREG, Merck's first-in-class hypoxia-inducible factor 2 alpha (HIF-2α) inhibitor, is an orally administered small-molecule that in conditions of hypoxia or impairment of VHL protein function, blocks HIF-2alpha and HIF-1beta interaction, which may reduce the transcription and expression of HIF-2α target genes associated with cellular proliferation, angiogenesis and tumor growth. By inhibiting HIF-2α signaling, WELIREG may disrupt key pathways certain tumors may use to adapt to low-oxygen conditions, including those that help promote abnormal blood vessel formation and support tumor survival.

WELIREG has received regulatory approvals in certain patients with advanced renal cell carcinoma with a clear cell component (ccRCC) and adjuvant ccRCC in combination with pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph, von Hippel-Lindau (VHL) disease-associated tumors and pheochromocytoma or paraganglioma (PPGL). As part of a broader clinical program, Merck continues to research WELIREG for people with RCC and selected solid tumors across different treatment settings, to further understand where WELIREG may provide clinical benefit.

Indications in the U.S.

von Hippel-Lindau disease

WELIREG is indicated for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic

neuroendocrine tumors (pNET), not requiring immediate surgery.

Renal Cell Carcinoma with a Clear Cell Component
WELIREG, in combination with pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph, is indicated for the adjuvant treatment of adult patients with renal cell carcinoma with a clear cell component (ccRCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

WELIREG, in combination with LENVIMA, is indicated for the treatment of adult patients with advanced ccRCC following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor.

WELIREG, as monotherapy, is indicated for the treatment of adult patients with advanced ccRCC following a PD-1 or PD-L1 inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

Pheochromocytoma or Paraganglioma
WELIREG is indicated for the treatment of adult and pediatric patients 12 years and older with locally advanced, unresectable, or metastatic pheochromocytoma or paraganglioma (PPGL).

Selected Safety Information for WELIREG

Warning: Embryo-Fetal Toxicity

Exposure to WELIREG during pregnancy can cause embryo-fetal harm. Verify pregnancy status prior to the initiation of WELIREG. Advise patients of these risks and the need for effective non-hormonal contraception as WELIREG can render some hormonal contraceptives ineffective.

Anemia

WELIREG can cause severe anemia that can require blood transfusion.

Monitor for anemia before initiation of, and periodically throughout, treatment with WELIREG. Transfuse patients as clinically indicated. Withhold, reduce dose, or permanently discontinue WELIREG based on severity.

In LITESPARK-004 (N=61), decreased hemoglobin occurred in 93% of patients with VHL disease and 7% had Grade 3 events. Median time to onset of anemia was 31 days (range: 1 day to 8.4 months).

The safety of erythropoiesis-stimulating agents (ESAs) for treatment of anemia in patients with VHL disease treated with WELIREG has not been established.

In LITESPARK-005, in patients receiving WELIREG for advanced ccRCC (n=372), decreased hemoglobin occurred in

88% of patients with advanced ccRCC and 29% had Grade 3 events. Median time to onset of anemia was 29 days (range: 1 day to 16.6 months). Of the patients with anemia, 22% received transfusions only, 20% received ESAs only, and 12% received both transfusion and ESAs.

In LITESPARK-022, in patients receiving WELIREG in combination with KEYTRUDA for adjuvant treatment for ccRCC (n=915), decreased hemoglobin occurred in 95% of patients and 11% had Grade 3 or higher events. Median time to onset of anemia was 42 days (range: 1 day to 11.1 months). Of the patients with anemia, 5% received transfusions only, 8% received erythropoiesis-stimulating agents (ESAs) only, and 1.3% received both transfusion and ESAs.

In LITESPARK-011, in patients receiving WELIREG in combination with LENVIMA for advanced ccRCC (n=370), decreased hemoglobin occurred in 87% of patients and 20% had Grade 3 events or required transfusion. Median time to onset of anemia was 56 days (range: 1 day to 33 months). Of the patients with anemia, 15% received transfusions only, 22% received erythropoiesis-stimulating agents (ESAs) only, and 8% received both transfusion and ESAs.

In LITESPARK-015 (n=72), anemia occurred in 96% of patients with PPGL and 22% had Grade 3 events. Median time to onset of anemia was 29 days (range: 1 day to 22.1 months). Of the patients with anemia, 20% received transfusions only, 26% received ESAs only, and 6% received both transfusion and ESAs.

Hypoxia

WELIREG can cause severe hypoxia that may require discontinuation, supplemental oxygen, or hospitalization.

Monitor oxygen saturation before initiation of, and periodically throughout, treatment with WELIREG. For decreased oxygen saturation with exercise (e.g., pulse oximeter <88% or PaO2 ≤55 mm Hg), consider withholding WELIREG until pulse oximetry with exercise is greater than 88%, then resume at the same or a reduced dose. For decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 ≤55 mm Hg) or when urgent intervention is indicated, withhold WELIREG until resolved and resume at a reduced dose or discontinue. For life-threatening or recurrent symptomatic hypoxia, permanently discontinue WELIREG. Advise patients to report signs and symptoms of hypoxia immediately to a health care provider.

In LITESPARK-004, hypoxia occurred in 1.6% of patients with VHL disease.

In LITESPARK-005, in patients receiving WELIREG for advanced ccRCC, hypoxia occurred in 15% of patients with advanced ccRCC and 10% had Grade 3 events. Of the patients with hypoxia, 69% were treated with oxygen therapy. Median time to onset of hypoxia was 30.5 days (range: 1 day to 21.1 months).

In LITESPARK-022, in patients receiving WELIREG in combination with KEYTRUDA for adjuvant treatment for ccRCC,

hypoxia occurred in 7% of patients receiving adjuvant treatment for ccRCC and 5% had Grade 3 or higher events. Of the patients with hypoxia, 47% were treated with oxygen therapy. Median time to onset of hypoxia was 93 days (range: 9 days to 11.7 months).

In LITESPARK-011, in patients receiving WELIREG in combination with LENVIMA for advanced ccRCC, hypoxia occurred in 16% of patients and 12% had Grade 3-4 events. Of the patients with hypoxia, 62% were treated with oxygen therapy. Median time to onset of hypoxia was 63 days (range: 4 days to 25 months).

In LITESPARK-015, hypoxia occurred in 13% of patients with PPGL and 10% had Grade 3 hypoxia. Median time to onset of hypoxia was 35 days (range: 6 days to 23.9 months). Of the patients with hypoxia, 67% were treated with oxygen therapy.

Cardiac Dysfunction with Concomitant Use of WELIREG and LENVIMA

Serious cardiac dysfunction, including heart failure with reduced left ventricular ejection fraction (LVEF), and cardiomyopathy, can occur with WELIREG in combination with LENVIMA. The safety of WELIREG in combination with LENVIMA has not been established in patients with LVEF below 50%.

In patients treated with WELIREG in combination with LENVIMA in the LITESPARK-011 trial, Grade 3 or higher cardiac dysfunction adverse events occurred in 6% of patients. The median time to onset of Grade 3 or higher of cardiac dysfunction was 26 weeks (range: 1 to 192 weeks). An absolute decrease in LVEF >20% with or without clinical symptoms occurred in 6% of patients. The median time to onset of LVEF decrease >20% was 29 weeks (range: 2 to 192 weeks).

Consider obtaining a baseline echocardiogram or Multigated Acquisition (MUGA) imaging. Monitor patients for symptoms or signs of heart failure and if present, reassess LVEF. Withhold and resume at a reduced dose upon recovery to baseline or Grade 1 or permanently discontinue WELIREG in combination with LENVIMA based on severity.

Embryo-Fetal Toxicity

Based on findings in animals, WELIREG can cause fetal harm when administered to a pregnant woman.

Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with WELIREG and for 1 week after the last dose. WELIREG can render some hormonal contraceptives ineffective. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with WELIREG and for 1 week after the last dose.

Adverse Reactions

Adverse Reactions in LITESPARK-004 (VHL disease)

Serious adverse reactions occurred in 15% of patients, including anemia, hypoxia, anaphylaxis reaction, retinal detachment, and central retinal vein occlusion (1 patient each).

WELIREG was permanently discontinued due to adverse reactions in 3.3% of patients for dizziness and opioid overdose (1.6% each).

Dosage interruptions due to an adverse reaction occurred in 39% of patients. Those which required dosage interruption in >2% of patients were fatigue, decreased hemoglobin, anemia, nausea, abdominal pain, headache, and influenza-like illness.

Dose reductions due to an adverse reaction occurred in 13% of patients. The most frequently reported adverse reaction which required dose reduction was fatigue (7%).

The most common adverse reactions (≥25%), including laboratory abnormalities, that occurred in patients who received WELIREG were decreased hemoglobin (93%), fatigue (64%), increased creatinine (64%), headache (39%), dizziness (38%), increased glucose (34%), and nausea (31%).

Adverse Reactions in LITESPARK-022 (Adjuvant ccRCC)

Serious adverse reactions occurred in 30% of patients receiving WELIREG in combination with KEYTRUDA. The most frequently reported serious adverse reactions (≥1%) were pneumonia (2%), hypoxia (1.9%), pneumonitis (1.6%), arrhythmia (1.5%), diarrhea (1.1%), and acute kidney injury (1.1%). Fatal adverse reactions occurred in 1.1% of patients who received WELIREG in combination with KEYTRUDA, including sepsis (0.1%).

WELIREG was permanently discontinued due to adverse reactions in 27% of patients. Adverse reactions which resulted in permanent discontinuation of WELIREG in ≥1% of patients included anemia (4%), fatigue (2.2%), rash (2%), increased alanine aminotransferase (ALT) (1.7%), hypoxia (1.6%), diarrhea (1.4%), pneumonitis (1.3%), increased aspartate aminotransferase (AST) (1.1%), and hepatic function abnormal (1%).

Dosage interruptions of WELIREG due to an adverse reaction occurred in 52% of patients. Of the patients who received WELIREG in combination with KEYTRUDA, 30% were ≥65 years old and 5% were ≥75 years old. Dose interruptions of WELIREG occurred in 57% of patients ≥65 years of age and in 49% of younger patients. Adverse reactions which required dosage interruption of WELIREG in ≥2% of patients included anemia (25%), fatigue (3.7%), increased ALT (3.5%), diarrhea (3.4%), increased AST (3.4%), COVID-19 (2.6%), hypoxia (2.5%), pyrexia (2.5%), musculoskeletal pain (2.1%), and rash (2.1%).

Dose reductions of WELIREG due to an adverse reaction occurred in 34% of patients. Dose reductions of WELIREG occurred in 39% of patients ≥65 years of age and in 32% of younger patients. Adverse reactions which required dose reduction in ≥3% of patients included anemia (17%), hypoxia (3.5%), increased ALT (3.2%), and fatigue (3.1%).

The most common (≥25%) adverse reactions, including laboratory abnormalities, in patients who received WELIREG in combination with KEYTRUDA were decreased hemoglobin (95%), increased ALT (57%), fatigue (49%), increased AST (46%), decreased lymphocytes (38%), and increased alkaline phosphatase (29%).

Adverse Reactions in LITESPARK-011 (Advanced ccRCC)

Serious adverse reactions occurred in 54% of patients who received WELIREG in combination with LENVIMA. Serious adverse reactions in ≥2% of patients included hypoxia (6%), pneumonia (5.0%), hyponatremia (3.2%), acute kidney injury (3%), hemorrhage (2.7%), anemia (2.7%), cardiac failure (2.4%), and diarrhea (2.4%). Fatal adverse reactions occurred in 5% of patients who received WELIREG in combination with LENVIMA, including sepsis (0.8%), pneumonia (0.5%), pneumonitis (0.5%), respiratory failure (0.5%), and one case (0.3%) each of acute cholecystitis, acute respiratory distress syndrome, pulmonary edema, embolic cerebral infarction, hemorrhage, postoperative wound complication, thrombotic microangiopathy, and upper respiratory tract infection.

Permanent discontinuation of WELIREG due to an adverse reaction occurred in 17% of patients. Adverse reactions which resulted in permanent discontinuation of WELIREG in >0.5% of patients included hypoxia (2.2%), pneumonia (1.1%), fatigue (0.8%), hyponatremia (0.8%), pneumonitis (0.8%), and respiratory failure (0.8%).

Dosage interruptions of WELIREG due to an adverse reaction occurred in 69% of patients. Adverse reactions which required dosage interruption in >3% of patients included fatigue (14%), diarrhea (12%), anemia (9%), vomiting (9%), hypertension (9%), nausea (8%), decreased appetite (5%), abdominal pain (4.6%), COVID-19 (4.6%), musculoskeletal pain (4.1%), pneumonia (3.5%), hypoxia (3.5%), and hemorrhage (3.5%).

Dose reductions of WELIREG due to an adverse reaction occurred in 35% of patients. Adverse reactions which required dose reductions in >2% of patients included fatigue (7%), hypoxia (7%), anemia (6%), diarrhea (3%), and dyspnea (2.4%).

The most common (≥25%) adverse reactions, including laboratory abnormalities, that occurred in patients who received WELIREG in combination with LENVIMA were decreased hemoglobin, fatigue, increased AST, hypertension, increased ALT, musculoskeletal pain, diarrhea, decreased lymphocytes, decreased sodium, increased creatinine, nausea, hypothyroidism, decreased appetite, decreased platelets, increased potassium, increased lipase, proteinuria, decreased magnesium, decreased calcium, increased activated partial thromboplastin time, rash, vomiting, decreased weight, constipation, abdominal pain, and stomatitis.

Adverse Reactions in LITESPARK-005 (Advanced ccRCC)

Serious adverse reactions occurred in 38% of patients. The most frequently reported serious adverse reactions (≥2%) were hypoxia (7%), anemia (5%), pneumonia (3.5%), hemorrhage (3%), and pleural effusion (2.2%). Fatal adverse reactions occurred in 3.2% of patients who received WELIREG, including sepsis (0.5%) and hemorrhage (0.5%).

WELIREG was permanently discontinued due to adverse reactions in 6% of patients. Adverse reactions which resulted in permanent discontinuation (≥0.5%) were hypoxia (1.1%), anemia (0.5%), and hemorrhage (0.5%).

Dosage interruptions due to an adverse reaction occurred in 39% of patients. Of the patients who received WELIREG, 28% were 65 to 74 years, and 10% were 75 years and over. Dose interruptions occurred in 48% of patients ≥65 years of age and in 34% of younger patients. Adverse reactions which required dosage interruption in ≥2% of patients were anemia (8%), hypoxia (5%), COVID-19 (4.3%), fatigue (3.2%), and hemorrhage (2.2%).

Dose reductions due to an adverse reaction occurred in 13% of patients. Dose reductions occurred in 18% of patients ≥65 years of age and in 10% of younger patients. The most frequently reported adverse reactions which required dose reduction (≥1%) were hypoxia (5%) and anemia (3.2%).

The most common adverse reactions (≥25%), including laboratory abnormalities, were decreased hemoglobin (88%), fatigue (43%), musculoskeletal pain (34%), increased creatinine (34%), decreased lymphocytes (34%), increased alanine aminotransferase (32%), decreased sodium (31%), increased potassium (29%), and increased aspartate aminotransferase (27%).

Adverse Reactions in LITESPARK-015 (PPGL)

Serious adverse reactions occurred in 36% of patients. The most frequently reported serious adverse reactions (≥2%) were anemia and hypertension (4.2% each) and pyelonephritis, pneumonia, hypoxia, dyspnea and hemorrhage (2.8% each).

WELIREG was permanently discontinued due to adverse reactions in 2 patients (2.8%). Adverse reactions which resulted in permanent discontinuation were increased alanine aminotransferase and paraparesis (1.4% each).

Dosage interruptions due to an adverse reaction occurred in 40% of patients. Of the patients who received WELIREG, 13% were ≥65 years old and 4.2% were ≥75 years. Adverse reactions which required dosage interruption in >3% of patients were hypoxia, nausea, and fatigue (4.2% each).

Dose reductions due to an adverse reaction occurred in 14% of patients. The most frequently reported adverse reaction which required dose reduction was hypoxia (4.2%).

The most common (≥25%) adverse reactions, including laboratory abnormalities, that occurred in patients were anemia (96%), fatigue (56%), musculoskeletal pain (56%), decreased lymphocytes (54%), increased alanine aminotransferase (51%), increased aspartate aminotransferase (42%), increased calcium (34%), dyspnea (33%), increased potassium (31%), decreased leukocytes (30%), headache (29%), increased alkaline phosphatase (25%), dizziness (26%) and nausea (25%).

Drug Interactions

Coadministration of WELIREG with inhibitors of UGT2B17 or CYP2C19 increases plasma exposure of belzutifan, which may increase the incidence and severity of adverse reactions. Monitor for anemia and hypoxia and reduce the dosage of WELIREG as recommended.

Coadministration of WELIREG with CYP3A4 substrates decreases concentrations of CYP3A4 substrates, which may reduce the efficacy of these substrates or lead to therapeutic failures. Avoid coadministration with sensitive CYP3A4 substrates. If coadministration cannot be avoided, increase the sensitive CYP3A4 substrate dosage in accordance with its Prescribing Information. Coadministration of WELIREG with hormonal contraceptives may lead to contraceptive failure or an increase in breakthrough bleeding.

Lactation

Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with WELIREG and for 1 week after the last dose.

Refer to the Prescribing Information of the individual therapeutic agents used in combination with WELIREG for lactation information. When used in combination, advise patients not to breastfeed during treatment and for the longest post-treatment duration recommended in the Prescribing Information of the individual products.

Females and Males of Reproductive Potential

WELIREG can cause fetal harm when administered to a pregnant woman. Verify the pregnancy status of females of reproductive potential prior to initiating treatment with WELIREG.

Use of WELIREG may reduce the efficacy of hormonal contraceptives. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with WELIREG and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with WELIREG and for 1 week after the last dose.

Based on findings in animals, WELIREG may impair fertility in males and females of reproductive potential and the reversibility of this effect is unknown.

Refer to the Prescribing Information of the individual therapeutic agents used in combination with WELIREG for pregnancy information.

Refer to the Prescribing Information of the individual therapeutic agents used in combination with WELIREG for contraception and infertility information. When used in combination, advise patients to use effective contraception during treatment and for the longest post-treatment duration recommended in the Prescribing Information of the individual products.

Pediatric Use

Use of WELIREG in pediatric patients aged 12 years and older for PPGL is supported by evidence from an adequate and well-controlled study of WELIREG in adults with additional pharmacokinetic data demonstrating that belzutifan exposure is predicted to be within range of that observed in adults, and that the course of locally advanced, unresectable, or metastatic pheochromocytoma or paraganglioma is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients.

The safety and effectiveness of WELIREG have not been established in pediatric patients with VHL or ccRCC, or in pediatric patients younger than 12 years of age with PPGL.

Renal Impairment

For patients with severe renal impairment (eGFR 15-29 mL/min estimated by MDRD), monitor for increased adverse reactions and modify the dosage as recommended.

Hepatic Impairment

For patients with moderate and severe hepatic impairment, monitor for increased adverse reactions and modify the dosage as recommended.

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

LENVIMA, discovered and developed by Eisai, is an orally available multiple receptor tyrosine 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, LENVIMA 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. The combination of LENVIMA and everolimus showed increased antiangiogenic and antitumor 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.

LENVIMA® (lenvatinib) Indications in the U.S.

- For the treatment of adult patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC).
- In combination with pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph, for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).
- In combination with belzutifan, for the treatment of adult patients with advanced renal cell carcinoma with a clear cell component (ccRCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor.
- In combination with everolimus, for the treatment of adult patients with advanced RCC following one prior anti-angiogenic therapy.
- For the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC).
- In combination with pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph, for the treatment of patients with advanced endometrial carcinoma (EC) that is mismatch repair proficient (pMMR) or not microsatellite instability-high (MSI-H), as determined by an FDA-authorized test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

Selected Safety Information for LENVIMA

Warnings and Precautions

Hypertension. In differentiated thyroid cancer (DTC), hypertension occurred in 73% of patients on LENVIMA (44% grade 3-4). In advanced renal cell carcinoma (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 unresectable hepatocellular carcinoma (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, including heart failure with reduced left ventricular ejection fraction (LVEF), and cardiomyopathy, can occur with LENVIMA. The safety of LENVIMA either as monotherapy or in combination with WELIREG has not been established in patients with LVEF below 50%. In patients with DTC, RCC, or HCC treated with LENVIMA, Grade 3 or higher cardiac dysfunction adverse events

occurred in 1% of patients. The median time to onset of Grade 3 or higher cardiac dysfunction was 35 weeks (range 7 to 63 weeks). An absolute decrease in LVEF >20% with or without clinical symptoms occurred in 1% of LENVIMA-treated patients. The median time to onset of LVEF decrease >20% was 33 weeks (range 4 to 83 weeks).

In patients treated with LENVIMA in combination with WELIREG for ccRCC, Grade 3 or higher cardiac dysfunction adverse events occurred in 6% of patients. The median time to onset of Grade 3 or higher cardiac dysfunction was 26 weeks (range 1 to 192 weeks). An absolute decrease in LVEF >20% with or without clinical symptoms occurred in 6% of patients and the median time to onset of LVEF decrease >20% was 29 weeks (range: 2 to 192 weeks).

Consider obtaining a baseline echocardiogram or Multigated Acquisition (MUGA) imaging. Monitor patients for symptoms or signs of heart failure and if present, reassess LVEF. Withhold and resume at a reduced dose upon recovery to baseline or Grade 1 or permanently discontinue LENVIMA 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.

Arterial thrombotic events of any severity occurred in 5% of patients with RCC receiving LENVIMA + KEYTRUDA, including myocardial infarction (3.4%) and cerebrovascular accident (2.3%).

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. Serious hepatic adverse reactions occurred in 1.4% of LENVIMA-treated patients with malignancies other than HCC. Fatal events, including hepatic failure, acute hepatitis and hepatorenal syndrome, occurred in 0.5% of patients. In HCC, hepatic encephalopathy occurred in 8% of LENVIMA-treated patients (5% Grade 3-5), and Grade 3-5 hepatic failure occurred in 3% of 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 adverse reactions including fatal renal failure or renal impairment, or thrombotic microangiopathy, 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 LENVIMA 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.

Diarrhea. In DTC and HCC, diarrhea occurred in 49% of LENVIMA-treated patients (6% Grade 3). In RCC, diarrhea occurred in 81% of LENVIMA + everolimus–treated patients (19% Grade 3). Diarrhea was the most frequent cause of dose interruption/reduction, and diarrhea recurred despite dose reduction. Promptly initiate management of diarrhea. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Fistula Formation and Gastrointestinal Perforation. In patients treated with LENVIMA or LENVIMA + everolimus in DTC, RCC, and HCC, fistula or gastrointestinal perforation occurred in 2%. Permanently discontinue in patients who develop gastrointestinal perforation of any severity or Grade 3-4 fistula.

QTc Interval Prolongation. In DTC, QT/QTc interval prolongation occurred in 9% of LENVIMA-treated patients and QTc 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 QTc interval. 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.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS). In 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 depending on severity and persistence of neurologic symptoms.

Hemorrhagic Events. Serious including fatal hemorrhagic events can occur with LENVIMA. In DTC, RCC, and HCC, hemorrhagic events, of any grade, occurred in 29% of patients treated with LENVIMA as a single agent or in combination with everolimus. The most frequently reported hemorrhagic events (≥5%) 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 with 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 ATC have not been established.

Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (eg, 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.

Impaired Wound Healing. Impaired wound healing has been reported in patients who received LENVIMA. Withhold LENVIMA for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of LENVIMA after resolution of wound healing complications has not been established.

Osteonecrosis of the Jaw (ONJ). ONJ has been reported in patients receiving LENVIMA. Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease or invasive dental procedures, may increase the risk of ONJ.

Perform an oral examination prior to treatment with LENVIMA and periodically during treatment. Advise patients regarding good oral hygiene practices.

Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk. Withhold LENVIMA for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ.

Withhold LENVIMA if ONJ develops and restart based on clinical judgement of adequate resolution.

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 LENVIMA 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 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, diarrhea (67% each), arthralgia/myalgia (62%), decreased appetite (54%), decreased weight (51%), nausea (47%), stomatitis (41%), headache (38%), vomiting (36%), proteinuria (34%), palmar-plantar erythrodysesthesia syndrome (32%), abdominal pain, and dysphonia (31% each). The most common serious adverse reactions (≥2%) were pneumonia (4%), hypertension, and dehydration (3% each). Adverse reactions led to dose reductions in 68% of LENVIMA-treated patients; 18% discontinued LENVIMA. The most common adverse reactions (≥10%) resulting in dose reductions were hypertension (13%), proteinuria (11%), decreased appetite, and diarrhea (10% each); the most common adverse reactions (≥1%) resulting in discontinuation of LENVIMA were hypertension and asthenia (1% each).

In RCC, the most common adverse reactions (≥20%) observed in LENVIMA + KEYTRUDA-treated patients were fatigue (63%), diarrhea (62%), musculoskeletal pain (58%), hypothyroidism (57%), hypertension (56%), stomatitis (43%), decreased appetite (41%), rash (37%), nausea (36%), decreased weight, dysphonia, proteinuria (30% each), palmar-plantar erythrodysesthesia syndrome (29%), abdominal pain, hemorrhagic events (27% each), vomiting (26%), constipation, hepatotoxicity (25% each), headache (23%), and acute kidney injury (21%).

Fatal adverse reactions occurred in 4.3% of patients receiving LENVIMA + 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 + KEYTRUDA; the most common (≥2%) were hemorrhagic events (5%), diarrhea (4%), hypertension, myocardial infarction, pneumonitis, vomiting (3% each), acute kidney injury, adrenal insufficiency, dyspnea, and pneumonia (2% each).

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

Dose interruptions of LENVIMA, KEYTRUDA, or both due to an adverse reaction occurred in 78% of patients receiving LENVIMA + KEYTRUDA. LENVIMA was interrupted in 73% of patients and both drugs 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 (11%), nausea, stomatitis (9% each), musculoskeletal pain, rash (8% each), increased lipase (7%), abdominal pain and vomiting (6% each), increased ALT, and increased amylase (5% each).

In RCC, the most common (≥25%) adverse reactions, that occurred in patients who received LENVIMA + WELIREG were anemia (70%), fatigue (68%), hypertension (60%), musculoskeletal pain (55%), diarrhea (54%), nausea, hypothyroidism, (42% each), decreased appetite (41%), proteinuria (38%), rash (33%), vomiting (32%), decreased weight (29%), constipation (27%), abdominal pain (26%), and stomatitis (25%).

Fatal adverse reactions occurred in 5% of patients who received LENVIMA + WELIREG, including sepsis (0.8%), pneumonia, pneumonitis, respiratory failure (0.5% each), and one case (0.3%) each of acute cholecystitis, acute respiratory distress syndrome, pulmonary edema, embolic cerebral infarction, hemorrhage, postoperative wound complication, thrombotic microangiopathy, and upper respiratory tract infection.

Serious adverse reactions (≥2%) included hypoxia (6%), pneumonia (5%), hyponatremia (3.2%), acute kidney injury (3%), hemorrhage, anemia (2.7% each), cardiac failure, and diarrhea (2.4% each).

Permanent discontinuation of LENVIMA due to an adverse reaction occurred in 23% of patients. Adverse reactions

which resulted in permanent discontinuation of LENVIMA in (>0.5%) of patients included fatigue (1.6%), cardiac failure, hyponatremia, pneumonia (1.1% each), decreased ejection fraction, increased lipase, pneumonitis, proteinuria, and rash (0.8% each).

Dosage interruptions of LENVIMA due to an adverse reaction occurred in 72% of patients. The most common adverse reactions requiring dose interruption (>3%) were fatigue (15%), hypertension (14%), diarrhea (13%), nausea, vomiting (10% each), anemia (8%), proteinuria (7%), decreased appetite (6%), COVID-19 (5%), musculoskeletal pain, abdominal pain, rash (4.3% each), pneumonia, stomatitis (3.5% each), and hemorrhage (3.2%).

Dose reductions of LENVIMA due to an adverse reaction occurred in 67% of patients. The most common adverse reactions which required dose reductions (>2%) were fatigue (20%), diarrhea (13%), hypertension (12%), proteinuria (9%), decreased appetite (8%), nausea, rash (6% each), vomiting (4.1%), anemia, decreased weight (3.5% each), abdominal pain (3%), increased ALT, stomatitis (2.7% each), musculoskeletal pain (2.4%), and hypothyroidism (2.2%).

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, peripheral edema (42% each), cough, abdominal pain (37% each), dyspnea, rash (35% each), 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, diarrhea, vomiting, and dyspnea (5% each). Adverse reactions led to dose reductions or interruption in 89% of patients. The most common adverse reactions (≥5%) resulting in dose reductions were diarrhea (21%), fatigue (8%), thrombocytopenia, vomiting (6% each), nausea, and proteinuria (5% each). Treatment discontinuation due to an adverse reaction occurred in 29% of patients.

In HCC, the most common adverse reactions (≥20%) observed in LENVIMA-treated patients were hypertension (45%), fatigue (44%), diarrhea (39%), decreased appetite (34%), arthralgia/myalgia, decreased weight (31% each), abdominal pain (30%), palmar-plantar erythrodysesthesia syndrome (27%), proteinuria (26%), dysphonia (24%), hemorrhagic events (23%), hypothyroidism (21%), and nausea (20%). The most common serious adverse reactions (≥2%) were hepatic encephalopathy (5%), hepatic failure, ascites (3% each), and decreased appetite (2%). Adverse reactions led to dose reductions or interruption in 62% of patients. The most common adverse reactions (≥5%) resulting in dose reductions or interruptions were fatigue (9%), decreased appetite, diarrhea (8% each), proteinuria (7%), hypertension (6%), and palmar-plantar erythrodysesthesia syndrome (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 hepatic encephalopathy (2%), fatigue (1%), hyperbilirubinemia, and hepatic failure (1% each).

In EC, the most common adverse reactions (≥20%) observed in LENVIMA + KEYTRUDA–treated patients were

hypothyroidism, hypertension (67% each), fatigue (58%), diarrhea (55%), musculoskeletal disorders (53%), nausea (49%), decreased appetite (44%), vomiting (37%), stomatitis (35%), decreased weight, abdominal pain (34% each), urinary tract infection (31%), proteinuria (29%), constipation (27%), headache (26%), hemorrhagic events (25%), palmar-plantar erythrodysesthesia (23%), dysphonia (22%), and rash (20%).

Fatal adverse reactions among these patients occurred in 4.7% of those treated with LENVIMA and KEYTRUDA, including 2 cases of pneumonia, and 1 case of the following: acute kidney injury, acute myocardial infarction, colitis, decreased appetite, intestinal perforation, lower gastrointestinal hemorrhage, malignant gastrointestinal obstruction, multiple organ dysfunction syndrome, myelodysplastic syndrome, pulmonary embolism, and right ventricular dysfunction.

Serious adverse reactions occurred in 50% of these patients receiving LENVIMA and KEYTRUDA. Serious adverse reactions with frequency ≥3% were hypertension (4.4%), and urinary tract infection (3.2%).

Discontinuation of LENVIMA due to an adverse reaction occurred in 26% of these patients. The most common (≥1%) adverse reactions leading to discontinuation of LENVIMA were hypertension (2%), asthenia (1.8%), diarrhea, decreased appetite, proteinuria, and vomiting (1.2% each).

Dose reductions of LENVIMA due to adverse reactions occurred in 67% of patients. The most common (≥5%) adverse reactions resulting in dose reduction of LENVIMA were hypertension (18%), diarrhea (11%), palmar-plantar erythrodysesthesia syndrome (9%), proteinuria, fatigue (7% each), decreased appetite (6%), asthenia, and weight decreased (5% each).

Dose interruptions of LENVIMA due to an adverse reaction occurred in 58% of these patients. The most common (≥2%) adverse reactions leading to interruption of LENVIMA were hypertension, diarrhea (11% each), proteinuria (6%), decreased appetite, vomiting (5% each), increased alanine aminotransferase, fatigue, nausea (3.5% each), abdominal pain (2.9%), weight decreased, urinary tract infection (2.6% each), increased aspartate aminotransferase, asthenia (2.3% each), and palmar-plantar erythrodysesthesia (2%).

Use in Specific Populations

Because of the potential for serious adverse reactions in breastfed children, advise women to discontinue breastfeeding during treatment and for 1 week after last dose.

Verify the pregnancy status of females of reproductive potential prior to initiating LENVIMA.

LENVIMA may impair fertility in males and females of reproductive potential.

No dose adjustment is recommended for patients with mild (creatinine clearance [CLcr] 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or EC and severe (CLcr 15-29 mL/min) renal impairment. Reduce the dose for patients with DTC, RCC, or EC 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 with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with DTC, RCC, or EC and mild or moderate hepatic impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or EC and severe hepatic impairment. Reduce the dose for patients with DTC, RCC, or endometrial carcinoma and severe hepatic impairment.

About the Merck and Eisai strategic collaboration

In March 2018, Eisai and Merck, known as MSD outside of 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 jointly develop, manufacture and commercialize LENVIMA, both as monotherapy and in combination with Merck's anti-PD-1 therapy, KEYTRUDA, and HIF-2α inhibitor, WELIREG.

Merck's focus on cancer

Every day, we follow the science as we work to discover innovations that can help patients, no matter what stage of cancer they have. As a leading oncology company, we are pursuing research where scientific opportunity and medical need converge, underpinned by our diverse pipeline of more than 20 novel mechanisms. With one of the largest clinical development programs across more than 25 tumor types, we strive to advance breakthrough science that will shape the future of oncology. By addressing barriers to clinical trial participation, screening and treatment, we work with urgency to reduce disparities and help ensure patients have access to high-quality cancer care. Our unwavering commitment is what will bring us closer to our goal of bringing life to more patients with cancer. For more information, visit **www.merck.com/research/oncology/**.

About Merck

At Merck, known as MSD outside of the United States and Canada, we are unified around our purpose: We use the power of leading-edge science to save and improve lives around the world. For more than 130 years, we have brought hope to humanity through the development of important medicines and vaccines. We aspire to be the premier research-intensive biopharmaceutical company in the world – and today, we are at the forefront of research to deliver innovative health solutions that advance the prevention and treatment of diseases in people and animals. We foster a diverse and inclusive global workforce and operate responsibly every day to enable a safe,

sustainable and healthy future for all people and communities. For more information, visit **www.merck.com** and connect with us on **X (formerly Twitter)**, **Facebook**, **Instagram**, **YouTube** and **LinkedIn**.

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

This news release of Merck & Co., Inc., Rahway, 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 candidates that the candidates 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 Annual Report on Form 10-K for the year ended December 31, 2025 and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (**www.sec.gov**).

Please see Prescribing Information, including information for the Boxed Warning about embryo-fetal toxicity, for WELIREG (belzutifan) at **https://www.merck.com/product/usa/pi_circulars/w/welireg/welireg_pi.pdf** and Medication Guide for WELIREG at **https://www.merck.com/product/usa/pi_circulars/w/welireg/welireg_mg.pdf**.

Please see Prescribing Information for LENVIMA (lenvatinib) at **http://www.lenvima.com/pdfs/prescribing-information.pdf**.

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