KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

GUIDE FOR *KEYTRUDA* + *LENVIMA*

Information about dosing, administration, ordering, and support

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab)

Severe and Fatal Immune-Mediated Adverse Reactions

- KEYTRUDA is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or the programmed death ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, can affect more than one body system simultaneously, and can occur at any time after starting treatment or after discontinuation of treatment. Important immune-mediated adverse reactions listed here may not include all possible severe and fatal immune-mediated adverse reactions.

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib)

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.

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.
Before prescribing LENVIMA, please read the accompanying Prescribing Information and Patient Information.

INDICATIONS FOR *KEYTRUDA + LENVIMA*

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

- KEYTRUDA, in combination with LENVIMA, is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).
- KEYTRUDA, in combination with LENVIMA, is indicated for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) as determined by an FDA-approved test or not microsatellite instability-high (MSI-H), who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

- Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Early identification and management are essential to ensure safe use of anti–PD-1/PD-L1 treatments. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.
- Withhold or permanently discontinue KEYTRUDA depending on severity of the immune-mediated adverse reaction. In general, if KEYTRUDA requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose adverse reactions are not controlled with corticosteroid therapy.

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

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.
- Among patients receiving LENVIMA with KEYTRUDA, arterial thrombotic events of any severity occurred in 5% of patients in CLEAR, 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.

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.
Before prescribing LENVIMA, please read the accompanying Prescribing Information and Patient Information.

DOSAGE AND **ADMINISTRATION FOR** *KEYTRUDA + LENVIMA*

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

DOSING

Advanced RCC

The recommended dose of KEYTRUDA is 200 mg administered after dilution as an intravenous infusion over 30 minutes every 3 weeks or 400 mg administered after dilution as an intravenous infusion over 30 minutes every 6 weeks in combination with LENVIMA 20 mg orally once daily taken with or without food at the same time each day until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months. After completing 2 years of combination therapy, LENVIMA may be administered as a single agent until disease progression or until unacceptable toxicity.

Dosage Modifications for Severe Renal Impairment

The recommended dosage of LENVIMA for patients with **advanced RCC** and **severe renal impairment** (creatinine clearance less than 30 mL/min calculated by Cockcroft-Gault equation using actual body weight) is **10 mg orally once daily**.

Dosage Modifications for Severe Hepatic Impairment

The recommended dosage of LENVIMA for patients with **advanced RCC** and **severe hepatic impairment** (Child-Pugh C) is **10 mg taken orally once daily**.

When administering KEYTRUDA in combination with LENVIMA, modify the dosage of one or both drugs as appropriate. Withhold, dose reduce, or discontinue LENVIMA in accordance with the instructions in the Prescribing Information for LENVIMA. Withhold or discontinue KEYTRUDA in accordance with the instructions in the Prescribing Information for KEYTRUDA. No dose reductions are recommended for KEYTRUDA.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

Immune-Mediated Pneumonitis

- KEYTRUDA can cause immune-mediated pneumonitis. The incidence is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.4% (94/2799) of patients receiving KEYTRUDA, including fatal (0.1%), Grade 4 (0.3%), Grade 3 (0.9%), and Grade 2 (1.3%) reactions. Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis led to permanent discontinuation of KEYTRUDA in 1.3% (36) and withholding in 0.9% (26) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence. Pneumonitis resolved in 59% of the 94 patients.

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

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 HCC, 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.

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the accompanying Prescribing Information and Patient Information.

DOSAGE AND **ADMINISTRATION FOR** ***KEYTRUDA + LENVIMA*** (*continued*)

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

DOSING

Advanced Endometrial Carcinoma

The recommended dose of KEYTRUDA is 200 mg administered after dilution as an intravenous infusion over 30 minutes every 3 weeks or 400 mg administered after dilution as an intravenous infusion over 30 minutes every 6 weeks in combination with LENVIMA 20 mg orally once daily taken with or without food at the same time each day until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months.

Dosage Modifications for Severe Renal Impairment

The recommended dosage of LENVIMA for patients with **advanced endometrial carcinoma** and **severe renal impairment** (creatinine clearance less than 30 mL/min calculated by Cockcroft-Gault equation using actual body weight) is **10 mg orally once daily**.

Dosage Modifications for Severe Hepatic Impairment

The recommended dosage of LENVIMA for patients with **advanced endometrial carcinoma** and **severe hepatic impairment** (Child-Pugh C) is **10 mg orally once daily**.

When administering KEYTRUDA in combination with LENVIMA, modify the dosage of one or both drugs as appropriate. Withhold, dose reduce, or discontinue LENVIMA in accordance with the instructions in the Prescribing Information for LENVIMA. Withhold or discontinue KEYTRUDA in accordance with the instructions in the Prescribing Information for KEYTRUDA. No dose reductions are recommended for KEYTRUDA.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

Immune-Mediated Colitis

- KEYTRUDA can cause immune-mediated colitis, which may present with diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 1.7% (48/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (1.1%), and Grade 2 (0.4%) reactions. Systemic corticosteroids were required in 69% (33/48); additional immunosuppressant therapy was required in 4.2% of patients. Colitis led to permanent discontinuation of KEYTRUDA in 0.5% (15) and withholding in 0.5% (13) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence. Colitis resolved in 85% of the 48 patients.

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

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.

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the accompanying Prescribing Information and Patient Information.

DOSAGE AND **ADMINISTRATION FOR** ***KEYTRUDA + LENVIMA*** (*continued*)

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

DOSAGE MODIFICATIONS FOR *KEYTRUDA*

- When administering KEYTRUDA and LENVIMA in combination, modify the dosage of one or both drugs as appropriate.
- Withhold or discontinue KEYTRUDA as shown on the following pages. No dose reductions for KEYTRUDA are recommended.
- In general, withhold KEYTRUDA for severe (Grade 3) immune-mediated adverse reactions.
- Permanently discontinue KEYTRUDA for:
  - Life-threatening (Grade 4) immune-mediated adverse reactions.
  - Recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment.
  - An inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.
- Dosage modifications for KEYTRUDA for adverse reactions that require management that differs from these general guidelines are summarized on pages 6–9.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, can affect more than one body system simultaneously, and can occur at any time after starting treatment or after discontinuation of treatment. Important immune-mediated adverse reactions listed here may not include all possible severe and fatal immune-mediated adverse reactions.

Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions.

- Early identification and management are essential to ensure safe use of anti–PD-1/PD-L1 treatments.
- Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
- In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection.
- Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue KEYTRUDA depending on severity of the immune-mediated adverse reaction.

- In general, if KEYTRUDA requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less.
- Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month.
- Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.
- Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (eg, endocrinopathies and dermatologic reactions) are discussed on the following pages.
- Additional monitoring and management considerations for selected immune-mediated adverse reactions are also discussed.

DOSAGE MODIFICATIONS FOR *KEYTRUDA* (*continued*)

Adverse Reaction	Severity[a]	Dosage Modification
Immune-mediated adverse reactions		
Pneumonitis	Grade 2	Withhold[b]
	Grades 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold[b]
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold[b]
	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue

[a]Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

[b]Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.

See additional dose modifications for KEYTRUDA on pages 7–9.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

Hepatotoxicity and Immune-Mediated Hepatitis

- KEYTRUDA can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (19/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.4%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 68% (13/19) of patients; additional immunosuppressant therapy was required in 11% of patients. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.2% (6) and withholding in 0.3% (9) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence. Hepatitis resolved in 79% of the 19 patients.

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

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

- Of the 737 LENVIMA-treated patients in DTC and HCC, diarrhea occurred in 49% (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.

DOSAGE MODIFICATIONS FOR *KEYTRUDA* (*continued*)

Adverse Reaction	Severity[a]	Dosage Modification
Immune-mediated adverse reactions (*continued*)		
Hepatitis with tumor involvement of the liver[b]	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold[c]
	ALT or AST increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with renal dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[c]
	Grade 4 increased blood creatinine	Permanently discontinue

[a]Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

[b]If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue KEYTRUDA based on recommendations for hepatitis with no liver involvement.

[c]Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.

See additional dose modifications for KEYTRUDA on pages 8 and 9.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

- KEYTRUDA can cause primary or secondary adrenal insufficiency. For Grade 2 or higher, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold KEYTRUDA depending on severity. Adrenal insufficiency occurred in 0.8% (22/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.3%) reactions. Systemic corticosteroids were required in 77% (17/22) of patients; of these, the majority remained on systemic corticosteroids. Adrenal insufficiency led to permanent discontinuation of KEYTRUDA in <0.1% (1) and withholding in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

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%. 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%.

QTc=corrected QT interval.

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the accompanying Prescribing Information and Patient Information.

DOSAGE MODIFICATIONS FOR *KEYTRUDA* (*continued*)

Adverse Reaction	Severity[a]	Dosage Modification
Immune-mediated adverse reactions (*continued*)		
Exfoliative dermatologic conditions	Suspected SJS, TEN, or DRESS	Withhold[b]
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological toxicities	Grade 2	Withhold[b]
	Grade 3 or 4	Permanently discontinue

[a]Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
[b]Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.
SJS=Stevens-Johnson syndrome; TEN=toxic epidermal necrolysis; DRESS=drug rash with eosinophilia and systemic symptoms.

See additional dose modifications for KEYTRUDA on page 9.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

Immune-Mediated Endocrinopathies (*continued*)

Hypophysitis

- KEYTRUDA can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as indicated. Withhold or permanently discontinue KEYTRUDA depending on severity. Hypophysitis occurred in 0.6% (17/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.2%) reactions. Systemic corticosteroids were required in 94% (16/17) of patients; of these, the majority remained on systemic corticosteroids. Hypophysitis led to permanent discontinuation of KEYTRUDA in 0.1% (4) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

QT Interval Prolongation (*continued*)

- 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.

DOSAGE MODIFICATIONS FOR *KEYTRUDA* (*continued*)

Adverse Reaction	Severity[a]	Dosage Modification
Immune-mediated adverse reactions (*continued*)		
Other Adverse Reactions		
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

[a]Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

Immune-Mediated Endocrinopathies (*continued*)

Thyroid Disorders

- KEYTRUDA can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue KEYTRUDA depending on severity. Thyroiditis occurred in 0.6% (16/2799) of patients receiving KEYTRUDA, including Grade 2 (0.3%). None discontinued, but KEYTRUDA was withheld in <0.1% (1) of patients.

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

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)

- 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 depending on severity and persistence of neurologic symptoms.

MRI=magnetic resonance imaging.

DOSAGE AND **ADMINISTRATION FOR** ***KEYTRUDA + LENVIMA*** (*continued*)

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Withhold, reduce, and/or discontinue LENVIMA based on the type and/or severity (grade) of the adverse reaction.

DOSAGE MODIFICATIONS FOR *LENVIMA* WHEN GIVEN WITH *KEYTRUDA* FOR ADVANCED RCC

- When administering KEYTRUDA in combination with LENVIMA, modify the dosage of one or both drugs as appropriate. Withhold, dose reduce, or discontinue LENVIMA as shown in this resource.
- Recommendations for adverse reaction management, including dose modifications, are included in the Prescribing Information for LENVIMA and outlined below and on the following pages.

Recommended dosage	First dosage reduction to	Second dosage reduction to	Third dosage reduction to
20 mg once daily	14 mg once daily	10 mg once daily	8 mg once daily

- The recommended dosage of LENVIMA for patients with **advanced RCC** and **severe renal impairment** (creatinine clearance less than 30 mL/min calculated by Cockcroft-Gault equation using actual body weight) is **10 mg orally once daily**.
- The recommended dosage of LENVIMA for patients with **advanced RCC** and **severe hepatic impairment** (Child-Pugh C) is **10 mg orally once daily**.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

Immune-Mediated Endocrinopathies (*continued*)

Thyroid Disorders (continued)

- Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (0.8%). It led to permanent discontinuation of KEYTRUDA in <0.1% (2) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Hypothyroidism occurred in 8% (237/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (6.2%). It led to permanent discontinuation of KEYTRUDA in <0.1% (1) and withholding in 0.5% (14) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. The majority of patients with hypothyroidism required long-term thyroid hormone replacement.

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

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 central nervous system (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.

DOSAGE AND **ADMINISTRATION FOR** *KEYTRUDA + LENVIMA* (*continued*)

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Withhold, reduce, and/or discontinue LENVIMA based on the type and/or severity (grade) of the adverse reaction.

DOSAGE MODIFICATIONS FOR *LENVIMA* WHEN GIVEN WITH *KEYTRUDA* FOR ADVANCED ENDOMETRIAL CARCINOMA

- When administering KEYTRUDA in combination with LENVIMA, modify the dosage of one or both drugs as appropriate. Withhold, dose reduce, or discontinue LENVIMA as shown in this resource.
- Recommendations for adverse reaction management, including dose modifications, are included in the Prescribing Information for LENVIMA and outlined below and on the following pages.

Recommended dosage	First dosage reduction to	Second dosage reduction to	Third dosage reduction to
20 mg once daily	14 mg once daily	10 mg once daily	8 mg once daily

- The recommended dosage of LENVIMA for patients with **advanced endometrial carcinoma** and **severe renal impairment** (creatinine clearance less than 30 mL/min calculated by Cockcroft-Gault equation using actual body weight) is **10 mg orally once daily**.
- The recommended dosage of LENVIMA for patients with **advanced endometrial carcinoma** and **severe hepatic impairment** (Child-Pugh C) is **10 mg orally once daily**.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

Immune-Mediated Endocrinopathies (*continued*)

Type 1 Diabetes Mellitus (DM), Which Can Present With Diabetic Ketoacidosis

- Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold KEYTRUDA depending on severity. Type 1 DM occurred in 0.2% (6/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in <0.1% (1) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

Hemorrhagic Events (*continued*)

- 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.

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the accompanying Prescribing Information and Patient Information.

RECOMMENDED ADVERSE REACTION MONITORING AND MANAGEMENT FOR *LENVIMA*

Adverse Reaction	Monitoring	Severity[a]	Dose Modifications
Hypertension *[see Warnings and Precautions]*	• 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.	Grade 3	• Withhold for Grade 3 that persists despite optimal antihypertensive therapy. • Resume at reduced dose when hypertension is controlled at less than or equal to Grade 2.
		Grade 4	• Permanently discontinue.
Cardiac dysfunction *[see Warnings and Precautions]*	• Monitor for clinical symptoms or signs of cardiac dysfunction.	Grade 3	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at a reduced dose or discontinue depending on the severity and persistence of adverse reaction.
		Grade 4	• Permanently discontinue.
Arterial thromboembolic events *[see Warnings and Precautions]*	• The safety of resuming LENVIMA 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.	Any Grade	• Permanently discontinue.
Hepatotoxicity *[see Warnings and Precautions]*	• 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.	Grade 3 or 4	• Withhold until improves to Grade 0 to 1 or baseline. • Either resume at a reduced dose or discontinue depending on severity and persistence of hepatotoxicity. • Permanently discontinue for hepatic failure.

[a]National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

See additional adverse reaction monitoring and management for LENVIMA on pages 13–17.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

Immune-Mediated Nephritis With Renal Dysfunction

- KEYTRUDA can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.3% (9/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 89% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.1% (3) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence. Nephritis resolved in 56% of the 9 patients.

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

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.

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the accompanying Prescribing Information and Patient Information.

RECOMMENDED ADVERSE REACTION MONITORING AND MANAGEMENT FOR *LENVIMA* (*continued*)

Adverse Reaction	Monitoring	Severity[a]	Dose Modifications
Renal failure or impairment *[see Warnings and Precautions]*	• Initiate prompt management of diarrhea or dehydration/ hypovolemia.	Grade 3 or 4	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at a reduced dose or discontinue depending on severity and persistence of renal impairment.
Proteinuria *[see Warnings and Precautions]*	• Monitor for proteinuria prior to initiation and periodically during treatment. – If urine dipstick proteinuria ≥2+ is detected, obtain a 24-hour urine protein.	2 g or greater proteinuria in 24 hours	• Withhold until less than or equal to 2 g of proteinuria per 24 hours. • Resume at a reduced dose. • Permanently discontinue for nephrotic syndrome.
Diarrhea *[see Warnings and Precautions]*	• Promptly initiate management of diarrhea.	Persistent or intolerable Grade 2 or 3 adverse reaction	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at reduced dose.
		Grade 4 adverse reaction	• Permanently discontinue.

[a]National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

See additional adverse reaction monitoring and management for LENVIMA on pages 14–17.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

Immune-Mediated Dermatologic Adverse Reactions

- KEYTRUDA can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms, and toxic epidermal necrolysis, has occurred with anti–PD-1/PD-L1 treatments. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 1.4% (38/2799) of patients receiving KEYTRUDA, including Grade 3 (1%) and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 40% (15/38) of patients. These reactions led to permanent discontinuation in 0.1% (2) and withholding of KEYTRUDA in 0.6% (16) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 6% had recurrence. The reactions resolved in 79% of the 38 patients.

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

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 LENVIMA treatment. Advise patients regarding good oral hygiene practices and to consider having preventive dentistry performed prior to treatment with LENVIMA and throughout treatment with LENVIMA.

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.
Before prescribing LENVIMA, please read the accompanying Prescribing Information and Patient Information.

RECOMMENDED ADVERSE REACTION MONITORING AND MANAGEMENT FOR *LENVIMA* (*continued*)

Adverse Reaction	Monitoring	Severity[a]	Dose Modifications
Gastrointestinal perforation *[see Warnings and Precautions]*		Any Grade	• Permanently discontinue.
Fistula formation *[see Warnings and Precautions]*		Grade 3 or 4	• Permanently discontinue.

[a]National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

See additional adverse reaction monitoring and management for LENVIMA on pages 15–17.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

Other Immune-Mediated Adverse Reactions

- The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received KEYTRUDA or were reported with the use of other anti–PD-1/PD-L1 treatments. Severe or fatal cases have been reported for some of these adverse reactions. *Cardiac/Vascular*: Myocarditis, pericarditis, vasculitis; *Nervous System*: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *Ocular*: Uveitis, iritis and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss; *Gastrointestinal*: Pancreatitis, to include increases in serum amylase and lipase levels, gastritis, duodenitis; *Musculoskeletal and Connective Tissue*: Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica; *Endocrine*: Hypoparathyroidism; *Hematologic/Immune*: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

Osteonecrosis of the Jaw (ONJ) (*continued*)

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 judgment 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.

RECOMMENDED ADVERSE REACTION MONITORING AND MANAGEMENT FOR *LENVIMA* (*continued*)

Adverse Reaction	Monitoring	Severity[a]	Dose Modifications
QT interval prolongation *[see Warnings and Precautions]*	• 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.	>500 ms or >60 ms increase from baseline	• Withhold until improves to less than or equal to 480 ms or baseline. • Resume at a reduced dose.
Hypocalcemia *[see Warnings and Precautions]*	• Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment.	Persistent or intolerable Grade 2 or 3 adverse reaction Grade 4 laboratory abnormality	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at reduced dose.
		Grade 4 adverse reaction	• Permanently discontinue.
Reversible posterior leukoencephalopathy syndrome (RPLS) *[see Warnings and Precautions]*	• Confirm diagnosis of RPLS with MRI.	Any Grade	• Withhold until fully resolved. • Resume at a reduced dose or discontinue depending on severity and persistence of neurologic symptoms.
Hemorrhagic events *[see Warnings and Precautions]*	• Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (eg, carotid artery).	Persistent or intolerable Grade 2 or 3 adverse reaction	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at reduced dose.
		Grade 4 adverse reaction	• Permanently discontinue.

[a]National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

See additional adverse reaction monitoring and management for LENVIMA on pages 16 and 17.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Infusion-Related Reactions

- KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 0.2% of 2799 patients receiving KEYTRUDA. Monitor for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion for Grade 1 or Grade 2 reactions. For Grade 3 or Grade 4 reactions, stop infusion and permanently discontinue KEYTRUDA.

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

Adverse Reactions

- 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 (30%), dysphonia (30%), proteinuria (30%), palmar-plantar erythrodysesthesia syndrome (29%), abdominal pain (27%), hemorrhagic events (27%), vomiting (26%), constipation (25%), hepatotoxicity (25%), headache (23%), and acute kidney injury (21%).

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the accompanying Prescribing Information and Patient Information.

RECOMMENDED ADVERSE REACTION MONITORING AND MANAGEMENT FOR *LENVIMA* (*continued*)

Adverse Reaction	Monitoring	Severity[a]	Dose Modifications
Impairment of thyroid-stimulating hormone suppression/ thyroid dysfunction *[see Warnings and Precautions]*	• Monitor thyroid function prior to initiation and at least monthly during treatment. • Treat hypothyroidism according to standard medical practice.		
Impaired wound healing *[see Warnings and Precautions]*	• The safety of resumption of LENVIMA after resolution of wound healing complications has not been established.		• 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.
Osteonecrosis of the jaw (ONJ) *[see Warnings and Precautions]*	• Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA treatment. • Advise patients regarding good oral hygiene practices. • Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk. • For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ.		• Withhold LENVIMA for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. • Withhold LENVIMA if ONJ develops and restart based on clinical judgement of adequate resolution.

[a]National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

See additional adverse reaction monitoring and management for LENVIMA on page 17.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

- Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after anti–PD-1/PD-L1 treatments. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute and chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between anti–PD-1/PD-L1 treatments and allogeneic HSCT. Follow patients closely for evidence of these complications and intervene promptly. Consider the benefit vs risks of using anti–PD-1/PD-L1 treatments prior to or after an allogeneic HSCT.

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

Adverse Reactions (*continued*)

Fatal adverse reactions occurred in 4.3% of patients receiving 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 and 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%).

RECOMMENDED ADVERSE REACTION MONITORING AND MANAGEMENT FOR *LENVIMA* (*continued*)

Adverse Reaction	Monitoring	Severity[a]	Dose Modifications
Other adverse reactions *[see Warnings and Precautions for Diarrhea, Hypocalcemia, and Hemorrhagic Events]*		Persistent or intolerable Grade 2 or 3 adverse reaction Grade 4 laboratory abnormality	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at reduced dose.
		Grade 4 adverse reaction	• Permanently discontinue.

[a]National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Increased Mortality in Patients With Multiple Myeloma

- In trials in patients with multiple myeloma, the addition of KEYTRUDA to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of these patients with an anti–PD-1/PD-L1 treatment in this combination is not recommended outside of controlled trials.

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

Adverse Reactions (*continued*)

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 drugs. The most common adverse reactions (≥2%) leading to permanent discontinuation of LENVIMA, KEYTRUDA, or both 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 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 (9%), stomatitis (9%), musculoskeletal pain (8%), rash (8%), increased lipase (7%), abdominal pain (6%), vomiting (6%), increased ALT (5%), and increased amylase (5%).

PREPARATION AND **ADMINISTRATION OF *KEYTRUDA***

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Preparation for Intravenous Infusion for KEYTRUDA

- Visually inspect the solution for particulate matter and discoloration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute KEYTRUDA injection (solution) prior to intravenous administration.
- Withdraw the required volume from the vial(s) of KEYTRUDA and transfer into an intravenous bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. **Mix diluted solution by gentle inversion.** Do not shake. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial.

Storage of Diluted Solution for KEYTRUDA

The product does not contain a preservative.

Store the diluted solution from the KEYTRUDA 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the diluted solution, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 96 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not shake.

Discard after 6 hours at room temperature or after 96 hours under refrigeration.

Do not freeze.

Administration for KEYTRUDA

- Administer diluted solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Embryofetal Toxicity

- Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Advise women of this potential risk. In females of reproductive potential, verify pregnancy status prior to initiating KEYTRUDA and advise them to use effective contraception during treatment and for 4 months after the last dose.

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

Adverse Reactions (*continued*)

- In endometrial carcinoma, the most common adverse reactions (≥20%) observed in LENVIMA + KEYTRUDA-treated patients were hypothyroidism (67%), hypertension (67%), fatigue (58%), diarrhea (55%), musculoskeletal disorders (53%), nausea (49%), decreased appetite (44%), vomiting (37%), stomatitis (35%), decreased weight (34%), abdominal pain (34%), urinary tract infection (31%), proteinuria (29%), constipation (27%), headache (26%), hemorrhagic events (25%), palmar-plantar erythrodysesthesia (23%), dysphonia (22%), and rash (20%).

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the accompanying Prescribing Information and Patient Information.

PREPARATION AND **ADMINISTRATION** OF *LENVIMA*

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Administration of LENVIMA

Oral: Capsule or Suspension

Capsule

- Swallow LENVIMA capsules whole at the same time each day with or without food.

Suspension

- Prepare oral suspension with water or apple juice and administer at the same time each day with or without food.

Feeding Tube Administration

Suspension

- Prepare suspension for feeding tube administration with water and administer at the same time each day with or without food.

Preparation of Suspension

- Place the required number of capsules, up to a maximum of 5, in a small container (approximately 20 mL capacity) or syringe (20 mL). Do not break or crush capsules.
- Add 3 mL of liquid to the container or syringe. Wait 10 minutes for the capsule shell (outer surface) to disintegrate, then stir or shake the mixture for 3 minutes until capsules are fully disintegrated and administer the entire contents.
- Next, add an additional 2 mL of liquid to the container or syringe using a second syringe or dropper, swirl or shake and administer. Repeat this step at least once and until there is no visible residue to ensure all of the medication is taken.
- If 6 capsules are required for a dose, follow these instructions using 3 capsules at a time.

If LENVIMA suspension is not used at the time of preparation, LENVIMA suspension may be stored in a refrigerator at 36°F to 46°F (2°C to 8°C) for a maximum of 24 hours in a covered container. If not administered within 24 hours, the suspension should be discarded.

Note: Compatibility has been confirmed for polypropylene syringes and for feeding tubes of at least 5 French diameter (polyvinyl chloride or polyurethane tube) and at least 6 French diameter (silicone tube).

- If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration.

Storage and Handling for LENVIMA

- Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

SELECTED SAFETY INFORMATION FOR *KEYTRUDA®* (pembrolizumab) (*continued*)

Adverse Reactions

- In KEYNOTE-581, when KEYTRUDA was administered in combination with LENVIMA to patients with advanced renal carcinoma (n=352), fatal adverse reactions occurred in 4.3% of patients. Serious adverse reactions occurred in 51% of patients; the most common (≥2%) were hemorrhagic events (5%), diarrhea (4%), hypertension, myocardial infarction, pneumonitis, and vomiting (3% each), acute kidney injury, adrenal insufficiency, dyspnea, and pneumonia (2% each).

SELECTED SAFETY INFORMATION FOR *LENVIMA®* (lenvatinib) (*continued*)

Adverse Reactions (*continued*)

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.

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the accompanying Prescribing Information and Patient Information.

NATIONAL DRUG CODES (NDCs) FOR *KEYTRUDA* + *LENVIMA*

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

NDC and Packaging Information

The NDC is typically required when submitting a claim with a miscellaneous Healthcare Common Procedure Coding System (HCPCS) code. Please consult with the payer to understand specific billing requirements.

PRODUCT	
KEYTRUDA® (pembrolizumab) Injection 100 mg	
PACKAGE	**NDC**
Carton containing one 100 mg/4 mL (25 mg/mL), single-dose vial	0006-3026-02
Carton containing two 100 mg/4 mL (25 mg/mL), single-dose vials	0006-3026-04

Please note: The NDCs above are the billable NDCs that appear on the cartons. The NDC on the vial should not be used for billing purposes.

Vial may not be shown at actual size.

PRODUCT	
LENVIMA® (lenvatinib) capsules	
PACKAGE	**NDC**
(24 mg) Carton with 6 cards (ten 10 mg capsules and five 4 mg capsules per card)	62856-724-30
(20 mg) Carton with 6 cards (ten 10 mg capsules per card)	62856-720-30
(18 mg) Carton with 6 cards (five 10 mg capsules and ten 4 mg capsules per card)	62856-718-30
(14 mg) Carton with 6 cards (five 10 mg capsules and five 4 mg capsules per card)	62856-714-30
(12 mg) Carton with 6 cards (fifteen 4 mg capsules per card)	62856-712-30
(10 mg) Carton with 6 cards (five 10 mg capsules per card)	62856-710-30
(8 mg) Carton with 6 cards (ten 4 mg capsules per card)	62856-708-30
(4 mg) Carton with 6 cards (five 4 mg capsules per card)	62856-704-30

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Adverse Reactions (*continued*)

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

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

Adverse Reactions (*continued*)

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%).

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the accompanying Prescribing Information and Patient Information.

BILLING CODES FOR *KEYTRUDA*

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Procedural Terminology (CPT®)[a] Code for Administration[1]

CPT CODE	DESCRIPTOR
96413	Injection and Intravenous Infusion Chemotherapy and Other Highly Complex Drug or Highly Complex Biologic Agent Administration

[a]CPT® is a registered trademark of the American Medical Association. Copyright 2022 American Medical Association. All rights reserved.
Please consult with the applicable payer to understand the payer's specific billing requirements.

HCPCS Code[2]

HCPCS CODE	DESCRIPTOR
J9271	Injection, pembrolizumab, 1 mg

Information about HCPCS codes is based on guidance issued by the Centers for Medicare & Medicaid Services applicable to Medicare Part B and may not apply to other public or private payers. Resources containing possible codes that could be relevant for KEYTRUDA and its administration are available from The Merck Access Program. Please visit merckaccessprogram-keytruda.com or call 855-257-3932 to speak with a representative (Monday through Friday, 8 AM to 8 PM ET). You are solely responsible for determining the appropriate codes and for any action you take in billing. Please consult with the applicable payer to understand the payer's specific billing requirements.

The information above may be relevant when billing for KEYTRUDA and its administration. This information is current as of March 2023. The information provided here is compiled from sources believed to be accurate, but Merck makes no representation that it is accurate. Consult the relevant manual and/or other guidelines for a description of each code to determine the appropriateness of its use and for information on additional codes. Diagnosis codes should be selected only by a health care professional. This information is subject to change. Merck cautions that payer-coding requirements vary and can frequently change, so it is important to regularly check with each payer or, where applicable, the Medicare Administrative Contractor as to payer-specific requirements.

The information provided here is not intended to be definitive or exhaustive, and is not intended to replace the guidance of a qualified professional advisor. Diagnosis codes should be selected only by a health care professional. Merck and its agents make no warranties or guarantees, expressed or implied, concerning the accuracy or appropriateness of this information for your particular use given the frequent changes in public and private payer billing. The use of this information does not guarantee payment or that any payment received will cover your costs.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Adverse Reactions (*continued*)

The most common adverse reactions (≥20%) observed with KEYTRUDA in combination with LENVIMA 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), palmar-plantar erythrodysesthesia syndrome (29%), abdominal pain and hemorrhagic events (27% each), vomiting (26%), constipation and hepatotoxicity (25% each), headache (23%), and acute kidney injury (21%).

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

Adverse Reactions (*continued*)

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 (1.2%), decreased appetite (1.2%), proteinuria (1.2%), and vomiting (1.2%).

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the accompanying Prescribing Information and Patient Information.

DISTRIBUTION INFORMATION FOR *KEYTRUDA* + *LENVIMA*

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Authorized Distributors for KEYTRUDA

AUTHORIZED DISTRIBUTOR	PHONE NUMBER	ORDER ITEM # FOR *KEYTRUDA* Carton of one 100 mg/4 mL (25 mg/mL), single-use vial	ORDER ITEM # FOR *KEYTRUDA* Carton of two 100 mg/4 mL (25 mg/mL), single-use vials
ASD Healthcare	800-746-6273	10248338	10246707
Besse Medical	800-543-2111	10254504	10251288
Cardinal Health Specialty Distribution	877-453-3972	5058029	5555008
CuraScript Specialty Distribution	877-599-7748	260622	386235
McKesson Plasma and Biologics	877-625-2566	3425493	3979275
McKesson Specialty Care Distribution	800-482-6700	5005010	5009280
Oncology Supply	800-633-7555	10239747	10242461

Merck does not recommend the use of one authorized distributor over another.

Merck does not make any warranty as to the services offered by any particular authorized distributor.

The Supplemental Return Program for Oncology Products is available to eligible customers for eligible products purchased from a distributor.
The program is subject to applicable conditions and restrictions. For information, please contact the Supplemental Returns Program for Oncology Products at 800-611-7397.

Authorized Distributors for LENVIMA

Questions about distribution of LENVIMA should be directed to Eisai.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Adverse Reactions (*continued*)

- In KEYNOTE-775, when KEYTRUDA was administered in combination with LENVIMA to patients with advanced endometrial carcinoma that was pMMR or not MSI-H (n=342), fatal adverse reactions occurred in 4.7% of patients. Serious adverse reactions occurred in 50% of these patients; the most common (≥3%) were hypertension (4.4%) and urinary tract infections (3.2%).

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

Adverse Reactions (*continued*)

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 (7%), fatigue (7%), decreased appetite (6%), asthenia (5%), and weight decreased (5%).

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.
Before prescribing LENVIMA, please read the accompanying Prescribing Information and Patient Information.

ACCESS AND ASSISTANCE PROGRAMS FOR *KEYTRUDA + LENVIMA*

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

The Merck Access Program for KEYTRUDA

may be able to help answer questions about:

- Benefit investigations
- Billing and coding
- Co-pay assistance for eligible patients
- Prior authorization and appeals process
- Referral to the Merck Patient Assistance Program for eligibility determination (provided through the Merck Patient Assistance Program, Inc.)
- Product distribution

For more information, visit merckaccessprogram-keytruda.com

For more information about access and support, call The Merck Access Program at 855-257-3932
(Monday to Friday, 8 AM to 8 PM ET)

The Eisai Assistance Program for LENVIMA

may be able to help answer questions about:

- Benefits and benefit investigations
- Insurance coverage
- Financial assistance options

For more information, visit eisaireimbursement.com

For more information about access and support, call the Eisai Assistance Program at 1-866-61-EISAI (1-866-613-4724)
(Monday to Friday, 8 AM to 8 PM ET)

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Adverse Reactions (*continued*)

Discontinuation of KEYTRUDA due to an adverse reaction occurred in 15% of these patients. The most common adverse reaction leading to discontinuation of KEYTRUDA (≥1%) was increased ALT (1.2%).

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

Adverse Reactions (*continued*)

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 (11%), diarrhea (11%), proteinuria (6%), decreased appetite (5%), vomiting (5%), increased alanine aminotransferase (3.5%), fatigue (3.5%), nausea (3.5%), abdominal pain (2.9%), weight decreased (2.6%), urinary tract infection (2.6%), increased aspartate aminotransferase (2.3%), asthenia (2.3%), and palmar-plantar erythrodysesthesia (2%).

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.
Before prescribing LENVIMA, please read the accompanying Prescribing Information and Patient Information.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*® (pembrolizumab) (*continued*)

Adverse Reactions (*continued*)

The most common adverse reactions for KEYTRUDA in combination with LENVIMA (reported in ≥20% patients) were hypothyroidism and hypertension (67% each), fatigue (58%), diarrhea (55%), musculoskeletal disorders (53%), nausea (49%), decreased appetite (44%), vomiting (37%), stomatitis (35%), abdominal pain and weight loss (34% each), urinary tract infections (31%), proteinuria (29%), constipation (27%), headache (26%), hemorrhagic events (25%), palmar-plantar erythrodysesthesia (23%), dysphonia (22%), and rash (20%).

Lactation

- Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 4 months after the last dose.

SELECTED SAFETY INFORMATION FOR *LENVIMA*® (lenvatinib) (*continued*)

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. 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 endometrial carcinoma and severe (CLcr 15-29 mL/min) renal impairment. Reduce the dose for patients with DTC, RCC, or endometrial carcinoma 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 endometrial carcinoma and mild or moderate hepatic impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or endometrial carcinoma and severe hepatic impairment. Reduce the dose for patients with DTC, RCC, or endometrial carcinoma and severe hepatic impairment.

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the accompanying Prescribing Information and Patient Information.

For prescribers: please click here for state-required price disclosures.

References: 1. AAPC Coder – CPT Code 96413. Accessed October 4, 2022. https://coder.aapc.com/cpt-codes/96413 **2.** CMS – 2020 Table of Drugs. https://www.cms.gov/Medicare/Coding/HCPCSReleaseCodeSets/Downloads/2020-Table-of-Drugs.pdf