GUIDE FOR *KEYTRUDA*

Information about dosing, administration, ordering, and support

SELECTED SAFETY INFORMATION FOR *KEYTRUDA*

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.
- 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.

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

KEYTRUDA®
(pembrolizumab) Injection 100 mg

INDICATIONS AND **USAGE FOR *KEYTRUDA***

- KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma.
- KEYTRUDA is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.
- KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non–small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.
- KEYTRUDA, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.
- KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 [tumor proportion score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is stage III where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic.
- KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.
- KEYTRUDA, in combination with platinum and FU, is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).
- KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [combined positive score (CPS) ≥1] as determined by an FDA-approved test.
- KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.
- KEYTRUDA is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL).
- KEYTRUDA is indicated for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.
- KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy. KEYTRUDA is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

See additional indications for KEYTRUDA on pages 3 and 4.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA* (*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.
- Pneumonitis occurred in 8% (31/389) of adult patients with cHL receiving KEYTRUDA as a single agent, including Grades 3-4 in 2.3% of patients. Patients received high-dose corticosteroids for a median duration of 10 days (range: 2 days to 53 months). Pneumonitis rates were similar in patients with and without prior thoracic radiation. Pneumonitis led to discontinuation of KEYTRUDA in 5.4% (21) of patients. Of the patients who developed pneumonitis, 42% interrupted KEYTRUDA, 68% discontinued KEYTRUDA, and 77% had resolution.

EGFR=epidermal growth factor receptor; ALK=anaplastic lymphoma kinase; FDA=Food and Drug Administration; FU=fluorouracil.

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

INDICATIONS AND **USAGE FOR *KEYTRUDA*** (*continued*)

- KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC):
  - who are not eligible for any platinum-containing chemotherapy, or
  - who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- KEYTRUDA is indicated for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.
- KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.
  This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.
- KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).
- KEYTRUDA, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.
  This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
  - in combination with platinum- and fluoropyrimidine-based chemotherapy, or
  - as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test.

See additional indications for KEYTRUDA on page 4.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA* (*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.

HER2=human epidermal growth factor receptor 2.

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

INDICATIONS AND **USAGE FOR *KEYTRUDA*** (*continued*)

- KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- KEYTRUDA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- KEYTRUDA is indicated for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC). This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).
- KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. The safety and effectiveness of KEYTRUDA in pediatric patients with TMB-H central nervous system cancers have not been established.
- KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC that is not curable by surgery or radiation.
- KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test.

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

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

Hepatotoxicity and Immune-Mediated Hepatitis

KEYTRUDA as a Single Agent

- 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.

KEYTRUDA With Axitinib

- KEYTRUDA in combination with axitinib can cause hepatic toxicity. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider monitoring more frequently as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt KEYTRUDA and axitinib, and consider administering corticosteroids as needed. With the combination of KEYTRUDA and axitinib, Grades 3 and 4 increased alanine aminotransferase (ALT) (20%) and increased aspartate aminotransferase (AST) (13%) were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. In patients with ALT ≥3 times upper limit of normal (ULN) (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Among the 92 patients who were rechallenged with either KEYTRUDA (n=3) or axitinib (n=34) administered as a single agent or with both (n=55), recurrence of ALT ≥3 times ULN was observed in 1 patient receiving KEYTRUDA, 16 patients receiving axitinib, and 24 patients receiving both. All patients with a recurrence of ALT ≥3 ULN subsequently recovered from the event.

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

DOSAGE AND **ADMINISTRATION FOR *KEYTRUDA***

Patient Selection for NSCLC, HNSCC, Esophageal Cancer, Cervical Cancer, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, TMB-H Cancer, or TNBC

Select patients for treatment with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression in:

- stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation.
- metastatic NSCLC.
- first-line treatment of metastatic or unresectable, recurrent HNSCC.
- previously treated recurrent locally advanced or metastatic esophageal cancer.
- recurrent or metastatic cervical cancer.

For the MSI-H/dMMR indications, select patients for treatment with KEYTRUDA as a single agent based on MSI-H/dMMR status in tumor specimens.

For the TMB-H indication, select patients for treatment with KEYTRUDA as a single agent based on TMB-H status in tumor specimens.

Because the effect of prior chemotherapy on test results for TMB-H, MSI-H, or dMMR in patients with high-grade gliomas is unclear, it is recommended to test for these markers in the primary tumor specimens obtained prior to initiation of temozolomide chemotherapy in patients with high-grade gliomas.

Patient Selection for Combination Therapy

For use of KEYTRUDA in combination with chemotherapy, select patients based on the presence of positive PD-L1 expression in locally recurrent unresectable or metastatic TNBC.

Additional Patient Selection Information

Information on FDA-approved tests used for patient selection is available at: http://www.fda.gov/CompanionDiagnostics.

- An FDA-approved test for the detection of MSI-H or dMMR is not currently available.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA* (*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.

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

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

FDA-Approved Dosing

Melanoma

The recommended dose of KEYTRUDA in adult patients with unresectable or metastatic melanoma is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks or 400 mg administered as an intravenous infusion over 30 minutes every 6 weeks until disease progression or unacceptable toxicity.

The recommended dose of KEYTRUDA for the adjuvant treatment of adult patients with melanoma is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks or 400 mg administered as an intravenous infusion over 30 minutes every 6 weeks until disease recurrence, unacceptable toxicity, or for up to 12 months.

NSCLC, HNSCC, Gastric Cancer, Esophageal Cancer

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks or 400 mg administered as an intravenous infusion over 30 minutes every 6 weeks until disease progression, unacceptable toxicity, or up to 24 months.

When administering KEYTRUDA in combination with chemotherapy, administer KEYTRUDA prior to chemotherapy when given on the same day. Refer to the Prescribing Information for the chemotherapy agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate.

MSI-H or dMMR CRC, Esophageal Cancer, Cervical Cancer, HCC, cSCC

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks or 400 mg administered as an intravenous infusion over 30 minutes every 6 weeks until disease progression, unacceptable toxicity, or up to 24 months.

cHL, PMBCL, MSI-H or dMMR Cancer, MCC, TMB-H Cancer

The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks or 400 mg administered as an intravenous infusion over 30 minutes every 6 weeks until disease progression, unacceptable toxicity, or up to 24 months.

The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg) administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months.

Urothelial Carcinoma

The recommended dose of KEYTRUDA in patients with locally advanced or metastatic urothelial carcinoma is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks or 400 mg administered as an intravenous infusion over 30 minutes every 6 weeks until disease progression, unacceptable toxicity, or up to 24 months.

The recommended dose of KEYTRUDA in patients with high-risk BCG-unresponsive NMIBC is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks or 400 mg administered as an intravenous infusion over 30 minutes every 6 weeks until persistent or recurrent high-risk NMIBC, disease progression, unacceptable toxicity, or up to 24 months.

See additional FDA-approved dosing for KEYTRUDA on page 7.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA* (*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.

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

FDA-Approved Dosing (*continued*)

RCC

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks or 400 mg administered as an intravenous infusion over 30 minutes every 6 weeks in combination with axitinib 5 mg orally twice daily until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months. When axitinib is used in combination with KEYTRUDA, dose escalation of axitinib above the initial 5-mg dose may be considered at intervals of 6 weeks or longer. See also the Prescribing Information for recommended axitinib dosing information.

TNBC

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks or 400 mg administered as an intravenous infusion over 30 minutes every 6 weeks until disease progression, unacceptable toxicity, or up to 24 months. When administering KEYTRUDA in combination with chemotherapy, administer KEYTRUDA prior to chemotherapy when given on the same day. Refer to the Prescribing Information for the chemotherapy agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate.

KEYTRUDA is indicated for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications. This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA* (*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.
- 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. The incidence of new or worsening hypothyroidism was higher in 1185 patients with HNSCC, occurring in 16% of patients receiving KEYTRUDA as a single agent or in combination with platinum and FU, including Grade 3 (0.3%) hypothyroidism. The incidence of new or worsening hypothyroidism was higher in 389 adult patients with cHL (17%) receiving KEYTRUDA as a single agent, including Grade 1 (6.2%) and Grade 2 (10.8%) hypothyroidism.

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.

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

DOSAGE MODIFICATIONS FOR *KEYTRUDA*

- 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 9-11.

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 on pages 9-11.

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

KEYTRUDA®
(pembrolizumab) Injection 100 mg

DOSAGE MODIFICATIONS FOR *KEYTRUDA* (*continued*)

Adverse Reaction	Severity[a]	Dose Modification for KEYTRUDA
Immune-Mediated Adverse Reactions		
Pneumonitis	Grade 2	Withhold[b]
	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold[b]
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) increases to more than 3 and up to 8 times upper limit of normal (ULN) or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold[b]
For liver enzyme elevations in patients treated with combination therapy with axitinib, see the additional table on page 11.	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.

See additional dosage modifications for KEYTRUDA on pages 10 and 11.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA* (*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.

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.

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

DOSAGE MODIFICATIONS FOR *KEYTRUDA* (*continued*)

Adverse Reaction	Severity[a]	Dose Modification for KEYTRUDA
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 dosage modifications for KEYTRUDA on page 11.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA* (*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.

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

DOSAGE MODIFICATIONS FOR *KEYTRUDA* (*continued*)

Adverse Reaction	Severity[a]	Dose Modification for KEYTRUDA
Exfoliative Dermatologic Conditions	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or drug rash with eosinophilia and systemic symptoms (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
Hematologic toxicity in patients with cHL or PMBCL	Grade 4	Withhold until resolution to Grades 0 or 1
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
[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.

RECOMMENDED SPECIFIC DOSAGE MODIFICATIONS FOR ADVERSE REACTIONS FOR COMBINATION

Treatment	Adverse Reaction	Severity	Dosage Modification
KEYTRUDA in combination with axitinib	Liver enzyme elevations[c]	ALT or AST increases to at least 3 times but less than 10 times ULN without concurrent total bilirubin at least 2 times ULN	Withhold both KEYTRUDA and axitinib until resolution to Grades 0 or 1[d]
		ALT or AST increases to more than 3 times ULN with concurrent total bilirubin at least 2 times ULN or ALT or AST ≥10 times ULN	Permanently discontinue both KEYTRUDA and axitinib

[c]Consider corticosteroid therapy
[d]Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Consider rechallenge with a single drug or sequential rechallenge with both drugs after recovery. If rechallenging with axitinib, consider dose reduction as per the axitinib Prescribing Information.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA* (*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.

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

PREPARATION AND **ADMINISTRATION FOR *KEYTRUDA***

Preparation for Intravenous Infusion

- 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

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

- 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* (*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.

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

KEYTRUDA®
(pembrolizumab) Injection 100 mg

NATIONAL DRUG CODES (NDCs) FOR *KEYTRUDA*

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.

SELECTED SAFETY INFORMATION FOR *KEYTRUDA* (*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.

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

BILLING CODES **FOR *KEYTRUDA***

Procedural Terminology (CPT®)[a] Code for Administration[1,2]

CPT CODE	DESCRIPTOR
96413 (Some payers may utilize 96365. Check with the applicable payer.)	Injection and Intravenous Infusion Chemotherapy and Other Highly Complex Drug or Highly Complex Biologic Agent Administration

[a]CPT Copyright 2020 American Medical Association. All rights reserved.
Please consult with the applicable payer to understand the payer's specific billing requirements.

HCPCS Code[3]

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 July 2021. 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* (*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.

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

DISTRIBUTION **INFORMATION FOR *KEYTRUDA***

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.

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

Adverse Reactions

- When KEYTRUDA was used as monotherapy, the most common adverse reactions (≥20%) were fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain.
- When KEYTRUDA was used in combination with chemotherapy, the most common adverse reactions (≥20%) were fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, stomatitis, headache, weight loss, abdominal pain, arthralgia, myalgia, and insomnia.
- When KEYTRUDA was used in combination with axitinib, the most common adverse reactions (≥20%) were diarrhea, fatigue/asthenia, hypertension, hepatotoxicity, hypothyroidism, decreased appetite, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation.

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

THE MERCK ACCESS PROGRAM AND NURSE EDUCATOR PROGRAM **FOR *KEYTRUDA***

The Merck Access Program 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)**.**

Nurse Educator Program

Nurse educators provide nurse-to-nurse staff education on appropriate dosing and administration of KEYTRUDA and information to help offices understand how to manage any potential adverse events.

For questions about KEYTRUDA, call 855-257-3932 to request an appointment with a nurse educator.

To learn more about KEYTRUDA, please visit keytrudahcp.com.

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

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 final dose.

Pediatric Use

- In KEYNOTE-051, 161 pediatric patients (62 pediatric patients aged 6 months to younger than 12 years and 99 pediatric patients aged 12 years to 17 years) were administered KEYTRUDA 2 mg/kg every 3 weeks. The median duration of exposure was 2.1 months (range: 1 day to 24 months).
- Adverse reactions that occurred at a ≥10% higher rate in pediatric patients when compared to adults were pyrexia (33%), vomiting (30%), leukopenia (30%), upper respiratory tract infection (29%), neutropenia (26%), headache (25%), and Grade 3 anemia (17%).

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

References: 1. AAPC Coder – CPT Code 96413. https://coder.aapc.com/cpt-codes/96413. Accessed April 3, 2020. **2.** AAPC Coder – CPT Code 96365. https://coder.aapc.com/cpt-codes/96365. Accessed April 3, 2020. **3.** CMS – 2020 Table of Drugs. https://www.cms.gov/Medicare/Coding/HCPCSReleaseCodeSets/Downloads/2020-Table-of-Drugs.pdf. Accessed April 3, 2020.

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KEYTRUDA® (pembrolizumab) Injection 100 mg