HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KEYTRUDA safely and effectively. See full prescribing information for KEYTRUDA.

KEYTRUDA® (pembrolizumab) for injection, for intravenous use
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE----------
KEYTRUDA is a human programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Administer 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks. (2.1)
- Reconstitute and dilute prior to intravenous infusion. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------
For injection: 50 mg, lyophilized powder in single-use vial for reconstitution (3)

----------CONTRAINDICATIONS----------
None. (4)

---------- WARNINGS AND PRECAUTIONS----------
- Immune-mediated adverse reactions: Administer corticosteroids based on the severity of the reaction. (5.1, 5.2, 5.3, 5.4, 5.5, 5.6)
  - Immune-mediated pneumonitis: Withhold for moderate, and permanently discontinue for severe or life-threatening pneumonitis. (5.1)
  - Immune-mediated colitis: Withhold for moderate or severe, and permanently discontinue for life-threatening colitis. (5.2)
  - Immune-mediated hepatitis: Monitor for changes in hepatic function. Based on severity of liver enzyme elevations, withhold or discontinue. (5.3)
  - Immune-mediated hypophysitis: Withhold for moderate, withhold or discontinue for severe, and permanently discontinue for life-threatening hypophysitis. (5.4)
  - Immune-mediated nephritis: Monitor for changes in renal function. Withhold for moderate, and permanently discontinue for severe or life-threatening nephritis. (5.5)
  - Immune-mediated hyperthyroidism and hypothyroidism: Monitor for changes in thyroid function. Withhold for severe and permanently discontinue for life-threatening hyperthyroidism. (5.6)
- Embryofetal Toxicity: KEYTRUDA may cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus. (5.8)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (reported in ≥20% of patients) included fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------
Nursing mothers: Discontinue nursing or discontinue KEYTRUDA. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor *[see Clinical Studies (14)]*.

This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of KEYTRUDA is 2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

2.2 Dose Modifications

Withhold KEYTRUDA for any of the following:

- Grade 2 pneumonitis *[see Warnings and Precautions (5.1)]*
- Grade 2 or 3 colitis *[see Warnings and Precautions (5.2)]*
- Symptomatic hypophysitis *[see Warnings and Precautions (5.4)]*
- Grade 2 nephritis *[see Warnings and Precautions (5.5)]*
- Grade 3 hyperthyroidism *[see Warnings and Precautions (5.6)]*
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
- Any other severe or Grade 3 treatment-related adverse reaction *[see Warnings and Precautions (5.7)]*

Resume KEYTRUDA in patients whose adverse reactions recover to Grade 0-1.

Permanently discontinue KEYTRUDA for any of the following:

- Any life-threatening adverse reaction
- Grade 3 or 4 pneumonitis *[see Warnings and Precautions (5.1)]*
- Grade 3 or 4 nephritis *[see Warnings and Precautions (5.5)]*
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN
  - For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week
- Grade 3 or 4 infusion-related reactions
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 adverse reactions that do not recover to Grade 0-1 within 12 weeks after last dose of KEYTRUDA
- Any severe or Grade 3 treatment-related adverse reaction that recurs *[see Warnings and Precautions (5.7)]*

2.3 Preparation and Administration

Preparation

- Add 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL).
- Slowly swirl the vial. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.
- Visually inspect the reconstituted solution for particulate matter and discoloration prior to administration. Reconstituted KEYTRUDA is a clear to slightly opalescent, colorless to slightly

yellow solution. Discard reconstituted vial if extraneous particulate matter other than translucent to white proteinaceous particles is observed.
- Withdraw the required volume from the vial(s) of KEYTRUDA and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP. Mix diluted solution by gentle inversion. 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 Reconstituted and Diluted Solutions
The product does not contain a preservative.
Store the reconstituted and diluted solutions of KEYTRUDA either:
- At room temperature for no more than 4 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Do not freeze.

Administration
- Administer infusion 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.

3 DOSAGE FORMS AND STRENGTHS

For injection: 50 mg lyophilized powder in a single-use vial for reconstitution

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis
Pneumonitis occurred in 12 (2.9%) of 411 melanoma patients, including Grade 2 or 3 cases in 8 (1.9%) and 1 (0.2%) patients, respectively, receiving KEYTRUDA in Trial 1. The median time to development of pneumonitis was 5 months (range 0.3 weeks-9.9 months). The median duration was 4.9 months (range 1 week-14.4 months). Five of eight patients with Grade 2 and the one patient with Grade 3 pneumonitis required initial treatment with high-dose systemic corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper. The median initial dose of high-dose corticosteroid treatment was 63.4 mg/day of prednisone or equivalent with a median duration of treatment of 3 days (range 1-34) followed by a corticosteroid taper. Pneumonitis led to discontinuation of KEYTRUDA in 3 (0.7%) patients. Pneumonitis completely resolved in seven of the nine patients with Grade 2-3 pneumonitis.

Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and administer corticosteroids for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) pneumonitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)].*

5.2 Immune-Mediated Colitis
Colitis (including microscopic colitis) occurred in 4 (1%) of 411 patients, including Grade 2 or 3 cases in 1 (0.2%) and 2 (0.5%) patients, respectively, receiving KEYTRUDA in Trial 1. The median time to onset of colitis was 6.5 months (range 2.3-9.8). The median duration was 2.6 months (range 0.6 weeks-3.6 months). All three patients with Grade 2 or 3 colitis were treated with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) with a median initial

dose of 70 mg/day of prednisone or equivalent; the median duration of initial treatment was 7 days (range 4-41), followed by a corticosteroid taper. One patient (0.2%) required permanent discontinuation of KEYTRUDA due to colitis. All four patients with colitis experienced complete resolution of the event.

Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)].*

5.3 Immune-Mediated Hepatitis

Hepatitis (including autoimmune hepatitis) occurred in 2 (0.5%) of 411 patients, including a Grade 4 case in 1 (0.2%) patient, receiving KEYTRUDA in Trial 1. The time to onset was 22 days for the case of Grade 4 hepatitis which lasted 1.1 months. The patient with Grade 4 hepatitis permanently discontinued KEYTRUDA and was treated with high-dose (greater than or equal to 40 mg prednisone or equivalent per day) systemic corticosteroids followed by a corticosteroid taper. Both patients with hepatitis experienced complete resolution of the event.

Monitor patients for changes in liver function. Administer corticosteroids for Grade 2 or greater hepatitis and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)].*

5.4 Immune-Mediated Hypophysitis

Hypophysitis occurred in 2 (0.5%) of 411 patients, consisting of one Grade 2 and one Grade 4 case (0.2% each), in patients receiving KEYTRUDA in Trial 1. The time to onset was 1.7 months for the patient with Grade 4 hypophysitis and 1.3 months for the patient with Grade 2 hypophysitis. Both patients were treated with high-dose (greater than or equal to 40 mg prednisone or equivalent per day) corticosteroids followed by a corticosteroid taper and remained on a physiologic replacement dose.

Monitor for signs and symptoms of hypophysitis. Administer corticosteroids for Grade 2 or greater hypophysitis. Withhold KEYTRUDA for moderate (Grade 2) hypophysitis, withhold or discontinue KEYTRUDA for severe (Grade 3) hypophysitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) hypophysitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)].*

5.5 Renal Failure and Immune-Mediated Nephritis

Nephritis occurred in 3 (0.7%) patients, consisting of one case of Grade 2 autoimmune nephritis (0.2%) and two cases of interstitial nephritis with renal failure (0.5%), one Grade 3 and one Grade 4. The time to onset of autoimmune nephritis was 11.6 months after the first dose of KEYTRUDA (5 months after the last dose) and lasted 3.2 months; this patient did not have a biopsy. Acute interstitial nephritis was confirmed by renal biopsy in two patients with Grades 3-4 renal failure. All three patients fully recovered renal function with treatment with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper.

Monitor patients for changes in renal function. Administer corticosteroids for Grade 2 or greater nephritis. Withhold KEYTRUDA for moderate (Grade 2) nephritis, and permanently discontinue KEYTRUDA for severe (Grade 3), or life-threatening (Grade 4) nephritis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)].*

5.6 Immune-Mediated Hyperthyroidism and Hypothyroidism

Hyperthyroidism occurred in 5 (1.2%) of 411 patients, including Grade 2 or 3 cases in 2 (0.5%) and 1 (0.2%) patients, respectively, receiving KEYTRUDA in Trial 1. The median time to onset was 1.5 months (range 0.5-2.1). The median duration was 2.8 months (range 0.9 to 6.1). One of two patients with Grade 2 and the one patient with Grade 3 hyperthyroidism required initial treatment with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper. One patient (0.2%) required permanent discontinuation of KEYTRUDA due to hyperthyroidism. All five patients with hyperthyroidism experienced complete resolution of the event.

Hypothyroidism occurred in 34 (8.3%) of 411 patients, including a Grade 3 case in 1 (0.2%) patient, receiving KEYTRUDA in Trial 1. The median time to onset of hypothyroidism was 3.5 months (range 0.7 weeks-19 months). All but two of the patients with hypothyroidism were treated with long-term thyroid hormone replacement therapy. The other two patients only required short-term thyroid hormone replacement therapy. No patient received corticosteroids or discontinued KEYTRUDA for management of hypothyroidism.

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

Administer corticosteroids for Grade 3 or greater hyperthyroidism, withhold KEYTRUDA for severe (Grade 3) hyperthyroidism, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) hyperthyroidism. Isolated hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)].*

5.7 Other Immune-Mediated Adverse Reactions

Other clinically important immune-mediated adverse reactions can occur.

The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of patients treated with KEYTRUDA in Trial 1: exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, and adrenal insufficiency.

Across clinical studies with KEYTRUDA in approximately 2000 patients, the following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients: myasthenic syndrome, optic neuritis, and rhabdomyolysis.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Restart KEYTRUDA if the adverse reaction remains at Grade 1 or less. Permanently discontinue KEYTRUDA for any severe or Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)].*

5.8 Embryofetal Toxicity

Based on its mechanism of action, KEYTRUDA may cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PDL-1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment with KEYTRUDA and for 4 months after the last dose of KEYTRUDA *[see Use in Specific Populations (8.1, 8.8)].*

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Immune-mediated pneumonitis *[see Warnings and Precautions (5.1)].*
- Immune-mediated colitis *[see Warnings and Precautions (5.2)]*.
- Immune-mediated hepatitis *[see Warnings and Precautions (5.3)]*.
- Immune-mediated hypophysitis *[see Warnings and Precautions (5.4)]*.
- Renal failure and immune-mediated nephritis *[see Warnings and Precautions (5.5)]*.
- Immune-mediated hyperthyroidism and hypothyroidism *[see Warnings and Precautions (5.6)]*.
- Immune-mediated adverse reactions *[see Warnings and Precautions (5.7)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the WARNINGS and PRECAUTIONS section reflect exposure to KEYTRUDA in Trial 1, an uncontrolled, open-label, multiple cohort trial in which 411 patients with unresectable or metastatic melanoma received KEYTRUDA at either 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks. The median duration of exposure to KEYTRUDA was 6.2 months (range 1 day to 24.6 months) with a median of 10 doses (range 1 to 51). The study population characteristics were: median age of 61 years (range 18-94), 39% age 65 years or older, 60% male, 97% white, 73% with M1c disease, 8% with brain metastases, 35% with elevated LDH, 54% with prior exposure to ipilimumab, and 47% with two or more prior systemic therapies for advanced or metastatic disease.

KEYTRUDA was discontinued for adverse reactions in 9% of the 411 patients. Adverse reactions, reported in at least two patients, that led to discontinuation of KEYTRUDA were: pneumonitis, renal failure, and pain. Serious adverse reactions occurred in 36% of patients receiving KEYTRUDA. The most frequent serious adverse drug reactions reported in 2% or more of patients in Trial 1 were renal failure, dyspnea, pneumonia, and cellulitis.

Table 1 presents adverse reactions identified from analyses of the 89 patients with unresectable or metastatic melanoma who received KEYTRUDA 2 mg/kg every three weeks in one cohort of Trial 1. Patients had documented disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. This cohort of Trial 1 excluded patients with severe immune-related toxicity related to ipilimumab, defined as any Grade 4 toxicity requiring treatment with corticosteroids or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; a medical condition that required systemic corticosteroids or other immunosuppressive medication; a history of pneumonitis or interstitial lung disease; or any active infection requiring therapy, including HIV or hepatitis B or C. Of the 89 patients in this cohort, the median age was 59 years (range 18-88), 33% were age 65 years or older, 53% were male, 98% were white, 44% had an elevated LDH, 84% had Stage M1c disease, 8% had brain metastases, and 70% received two or more prior therapies for advanced or metastatic disease. The median duration of exposure to KEYTRUDA was 6.2 months (range 1 day to 15.3 months) with a median of nine doses (range 1 to 23). Fifty-one percent of patients were exposed to KEYTRUDA for greater than 6 months and 21% for greater than 1 year.

KEYTRUDA was discontinued for adverse reactions in 6% of the 89 patients.The most common adverse reactions (reported in at least 20% of patients) were fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea.

Table 1: Adverse Reactions in ≥10% of Patients with Unresectable or Metastatic Melanoma

	KEYTRUDA 2 mg/kg every 3 weeks N=89	
Adverse Reaction	All Grades (%)	Grade 3* (%)
General Disorders and Administration Site Conditions		
Fatigue	47	7
Peripheral Edema	17	1
Chills	14	0
Pyrexia	11	0
Gastrointestinal Disorders		
Nausea	30	0
Constipation	21	0
Diarrhea	20	0
Vomiting	16	0
Abdominal pain	12	0
Respiratory, Thoracic And Mediastinal Disorders		
Cough	30	1
Dyspnea	18	2
Skin And Subcutaneous Tissue Disorders		
Pruritus	30	0
Rash	29	0
Vitiligo	11	0
Metabolism and Nutrition Disorders		
Decreased appetite	26	0
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	20	0
Pain in extremity	18	1
Myalgia	14	1
Back pain	12	1
Nervous System Disorders		
Headache	16	0
Dizziness	11	0
Blood and Lymphatic System Disorders		
Anemia	14	5
Psychiatric Disorders		
Insomnia	14	0
Infections and Infestations		
Upper respiratory tract infection	11	1

* There were no Grade 5 adverse reactions reported. Of the ≥10% adverse reactions, none was reported as Grade 4.

Other clinically important adverse reactions observed in up to 10% of patients treated with KEYTRUDA were:

Infections and infestations: sepsis

Table 2: Laboratory Abnormalities Increased from Baseline in ≥20% of Patients with Unresectable or Metastatic Melanoma

	KEYTRUDA 2 mg/kg every 3 weeks N=89	
Laboratory Test	**All Grades %**	**Grades 3-4 %**
Chemistry		
Hyperglycemia	40	2*
Hyponatremia	35	9
Hypoalbuminemia	34	0
Hypertriglyceridemia	25	0
Increased Aspartate Aminotransferase	24	2*
Hypocalcemia	24	1
Hematology		
Anemia	55	8*

* Grade 4 abnormalities in this table limited to hyperglycemia, increased aspartate aminotransferase, and anemia (one patient each)

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. Because trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results, a subset analysis was performed in the patients with a concentration of pembrolizumab below the drug tolerance level of the anti-product antibody assay. In this analysis, none of the 97 patients who were treated with 2 mg/kg every 3 weeks tested positive for treatment-emergent anti-pembrolizumab antibodies.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to KEYTRUDA with the incidences of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No formal pharmacokinetic drug interaction studies have been conducted with KEYTRUDA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D.

Risk Summary

Based on its mechanism of action, KEYTRUDA may cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PDL-1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.

Animal Data

Animal reproduction studies have not been conducted with KEYTRUDA to evaluate its effect on reproduction and fetal development, but an assessment of the effects on reproduction was provided. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering KEYTRUDA during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 knockout mice.

Human IgG4 (immunoglobulins) are known to cross the placenta; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. Based on its mechanism of action, fetal exposure to pembrolizumab may increase the risk of developing immune-mediated disorders or of altering the normal immune response.

8.3 Nursing Mothers
It is not known whether KEYTRUDA is excreted in human milk. No studies have been conducted to assess the impact of KEYTRUDA on milk production or its presence in breast milk. Because many drugs are excreted in human milk, instruct women to discontinue nursing during treatment with KEYTRUDA.

8.4 Pediatric Use
Safety and effectiveness of KEYTRUDA have not been established in pediatric patients.

8.5 Geriatric Use
Of the 411 patients treated with KEYTRUDA, 39% were 65 years and over. No overall differences in safety or efficacy were reported between elderly patients and younger patients.

8.6 Renal Impairment
Based on a population pharmacokinetic analysis, no dose adjustment is needed for patients with renal impairment *[see Clinical Pharmacology (12.3)].*

8.7 Hepatic Impairment
Based on a population pharmacokinetic analysis, no dose adjustment is needed for patients with mild hepatic impairment [total bilirubin (TB) less than or equal to ULN and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST]. KEYTRUDA has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment *[see Clinical Pharmacology (12.3)].*

8.8 Females and Males of Reproductive Potential
Based on its mechanism of action, KEYTRUDA may cause fetal harm when administered to a pregnant woman *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)].* Advise females of reproductive potential to use highly effective contraception during treatment with KEYTRUDA and for at least 4 months following the last dose of pembrolizumab.

10 OVERDOSAGE

There is no information on overdosage with KEYTRUDA.

11 DESCRIPTION

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

KEYTRUDA is a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial is reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate-80 (0.4 mg), sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the

anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

12.3 Pharmacokinetics

The pharmacokinetics of pembrolizumab was studied in 479 patients who received doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Based on a population pharmacokinetic analysis, the mean [% coefficient of variation (CV%)] clearance (CL) is 0.22 L/day (28%) and the mean (CV%) elimination half-life ($t_{1/2}$) is 26 days (24%). Steady-state concentrations of pembrolizumab were reached by 18 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve at steady state (AUC_{ss}) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

Specific Populations: The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The CL of pembrolizumab increased with increasing body weight; the resulting exposure differences were adequately addressed by the administration of a weight-based dose. The following factors had no clinically important effect on the CL of pembrolizumab: age (range 18-94 years), gender, renal impairment, mild hepatic impairment, and tumor burden. The effect of race could not be assessed due to limited data available in non-White patients.

Renal Impairment: The effect of renal impairment on the CL of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild (eGFR 60 to 89 mL/min/1.73 m^2; n=210), moderate (eGFR 30 to 59 mL/min/1.73m^2; n=43), or severe (eGFR 15 to 29 mL/min/1.73m^2; n=2) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73m^2; n=221) renal function. No clinically important differences in the CL of pembrolizumab were found between patients with renal impairment and patients with normal renal function *[see Use in Specific Populations (8.6)].*

Hepatic Impairment: The effect of hepatic impairment on the CL of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild hepatic impairment (TB less than or equal to ULN and AST greater than ULN or TB between 1 and 1.5 times ULN and any AST; n=59) compared to patients with normal hepatic function (TB and AST less than or equal to ULN; n=410). No clinically important differences in the CL of pembrolizumab were found between patients with mild hepatic impairment and normal hepatic function. KEYTRUDA has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment *[see Use in Specific Populations (8.7)].*

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to test the potential of pembrolizumab for carcinogenicity or genotoxicity.

Fertility studies have not been conducted with pembrolizumab. In 1-month and 6-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1 signaling resulted in an increased incidence of infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus (LCMV). Administration of pembrolizumab in chimpanzees with naturally occurring chronic hepatitis B infection resulted in two out of

four animals with significantly increased levels of serum ALT, AST, and GGT, which persisted for at least 1 month after discontinuation of pembrolizumab.

14 CLINICAL STUDIES

The efficacy of KEYTRUDA was investigated in a multicenter, open-label, randomized (1:1), dose-comparative, activity-estimating cohort of Trial 1. Key eligibility criteria were unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. The trial excluded patients with autoimmune disease; a medical condition that required immunosuppression; and a history of severe immune-mediated adverse reactions with ipilimumab, defined as any Grade 4 toxicity requiring treatment with corticosteroids or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks. Patients were randomized to receive 2 mg/kg (n=89) or 10 mg/kg (n=84) of KEYTRUDA every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Assessment of tumor status was performed every 12 weeks. The major efficacy outcome measures were confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by blinded independent central review and duration of response.

Among the 173 patients enrolled, the median age was 61 years (36% age 65 or older); 60% male; 97% White; and 66% and 34% with an ECOG performance status 0 and 1, respectively. Disease characteristics were BRAF V600 mutation (17%), elevated lactate dehydrogenase (39%), M1c (82%), brain metastases (9%), and two or more prior therapies for advanced or metastatic disease (73%).

The ORR was 24% (95% confidence interval: 15, 34) in the 2 mg/kg arm, consisting of 1 complete response and 20 partial responses. Among the 21 patients with an objective response, 3 (14%) had progression of disease 2.8, 2.9, and 8.2 months after initial response. The remaining 18 patients (86%) had ongoing responses with durations ranging from 1.4+ to 8.5+ months, which included 8 patients with ongoing responses of 6 months or longer. One additional patient developed two new asymptomatic lesions at the first tumor assessment concurrent with a 75% decrease in overall tumor burden; KEYTRUDA was continued and this reduction in tumor burden was durable for 5+ months.

There were objective responses in patients with and without BRAF V600 mutation-positive melanoma. Similar ORR results were observed in the 10 mg/kg arm.

16 HOW SUPPLIED/STORAGE AND HANDLING

KEYTRUDA is supplied in a carton containing one 50 mg single-use vial (NDC 0006-3029-02).

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

- Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA, including:
  - Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
  - Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.2)]*.
  - Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (5.3)]*.
  - Hypophysitis: Advise patients to contact their healthcare provider immediately for persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes *[see Warnings and Precautions (5.4)]*.

- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis *[see Warnings and Precautions (5.5)]*.
- Hyperthyroidism and Hypothyroidism: Advise patients to contact their healthcare provider immediately for signs or symptoms of hyperthyroidism and hypothyroidism *[see Warnings and Precautions (5.6)]*.

- Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests *[see Warnings and Precautions (5.3, 5.5, 5.6)]*.
- Advise women that KEYTRUDA may cause fetal harm. Instruct women of reproductive potential to use highly effective contraception during and for 4 months after the last dose of KEYTRUDA *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1, 8.8)]*.
- Advise nursing mothers not to breastfeed while taking KEYTRUDA *[see Use in Specific Populations (8.3)]*.

Manufactured by: Merck Sharp & Dohme Corp., a subsidiary of

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA
U.S. License No. 0002

At:
Schering-Plough (Brinny) Co.,
County Cork, Ireland

For patent information: www.merck.com/product/patent/home.html

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MEDICATION GUIDE
KEYTRUDA® (key-true-duh)
(pembrolizumab)
for injection

What is the most important information I should know about KEYTRUDA?

KEYTRUDA is a medicine that may treat your melanoma by working with your immune system. KEYTRUDA can cause your immune system to attack normal organs and tissues in many areas of your body and can affect the way they work. These problems can sometimes become serious or life-threatening.

Call or see your doctor right away if you develop any symptoms of the following problems or these symptoms get worse:

- **Lung problems (pneumonitis). Symptoms of pneumonitis may include:**
  - shortness of breath
  - chest pain
  - new or worse cough

- **Intestinal problems (colitis) that can lead to tears or holes in your intestine. Signs and symptoms of colitis may include:**
  - diarrhea or more bowel movements than usual
  - stools that are black, tarry, sticky, or have blood or mucus
  - severe stomach-area (abdomen) pain or tenderness

- **Liver problems (hepatitis). Signs and symptoms of hepatitis may include:**
  - yellowing of your skin or the whites of your eyes
  - dark urine
  - nausea or vomiting
  - feeling less hungry than usual
  - pain on the right side of your stomach area (abdomen)
  - bleeding or bruising more easily than normal

- **Hormone gland problems (especially the thyroid, pituitary, and adrenal glands). Signs and symptoms that your hormone glands are not working properly may include:**
  - rapid heart beat
  - weight loss
  - increased sweating
  - weight gain
  - hair loss
  - feeling cold

- constipation
- your voice gets deeper
- muscle aches
- dizziness or fainting
- headaches that will not go away or unusual headache

- **Kidney problems, including nephritis and kidney failure. Signs of kidney problems may include:**
  - change in the amount or color of your urine.

- **Problems in other organs. Signs of these problems may include:**
  - rash
  - changes in eyesight
  - severe or persistent muscle or joint pains
  - severe muscle weakness

Getting medical treatment right away may help keep these problems from becoming more serious.

Your doctor will check you for these problems during treatment with KEYTRUDA. Your doctor may treat you with corticosteroid medicines and delay or completely stop treatment with KEYTRUDA, if you have severe side effects.

What is KEYTRUDA?

KEYTRUDA is a prescription medicine used to treat a kind of skin cancer called melanoma. KEYTRUDA may be used when your melanoma:

- has spread or cannot be removed by surgery (advanced melanoma)
  and,
- after you have tried a medicine called ipilimumab and it did not work or is no longer working
  and,
- if your tumor has an abnormal "BRAF" gene, and you also have tried a different medicine called a BRAF inhibitor, and it did not work or is no longer working.

It is not known if KEYTRUDA is safe and effective in children less than 18 years of age.

What should I tell my doctor before receiving KEYTRUDA?

Before you receive KEYTRUDA, tell your doctor if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung or breathing problems
- have liver problems
- have any other medical problems
- are pregnant or plan to become pregnant.
  - KEYTRUDA may harm your unborn baby.
  - Females who are able to become pregnant should use an effective method of birth control during and for at least 4 months after the last dose of KEYTRUDA. Talk to your doctor about birth control methods that you can use during this time.
  - Tell your doctor right away if you become pregnant during treatment with KEYTRUDA.
- are breastfeeding or plan to breastfeed.
  - It is not known if KEYTRUDA passes into your breast milk.
  - Do not breastfeed during treatment with KEYTRUDA.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How will I receive KEYTRUDA?

- Your doctor will give you KEYTRUDA into your vein through an intravenous (IV) line over 30 minutes.
- KEYTRUDA is usually given every 3 weeks.
- Your doctor will decide how many treatments you need.
- Your doctor will do blood tests to check you for side effects.
- If you miss any appointments, call your doctor as soon as possible to reschedule your appointment.

What are the possible side effects of KEYTRUDA?

KEYTRUDA can cause serious side effects. See "What is the most important information I should know about KEYTRUDA?"

The most common side effects of KEYTRUDA include:

- feeling tired
- cough

- nausea
- itching
- rash
- decreased appetite
- constipation
- diarrhea
- joint pain

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of KEYTRUDA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of KEYTRUDA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about KEYTRUDA, talk with your doctor. You can ask your doctor or nurse for information about KEYTRUDA that is written for healthcare professionals. For more information, go to www.keytruda.com.

What are the ingredients in KEYTRUDA?

Active ingredient: pembrolizumab
Inactive ingredients: L-histidine, polysorbate-80, sucrose. May contain hydrochloric acid/sodium hydroxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA
U.S. License No. 0002

At:
Schering-Plough (Brinny) Co.,
County Cork, Ireland

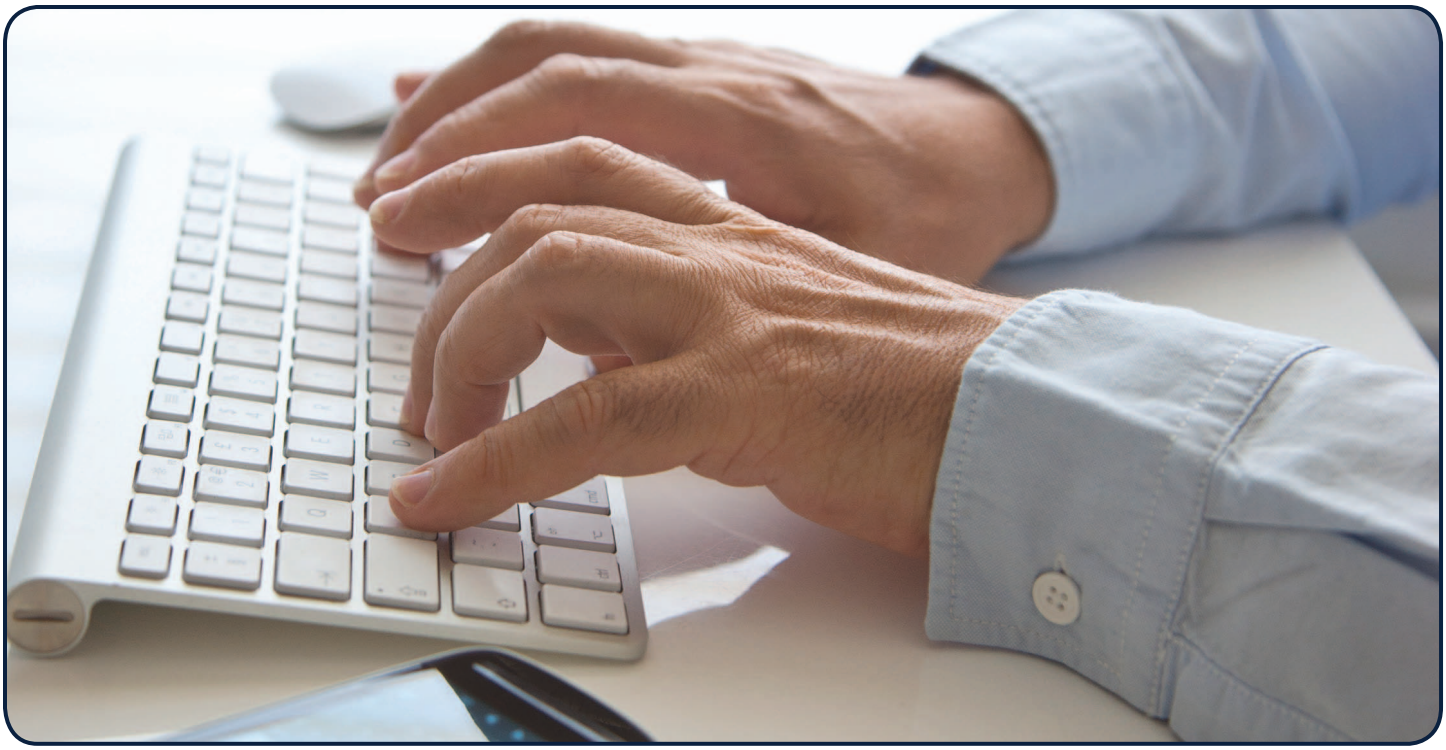
Issued: September 2014

For patent information: www.merck.com/product/patent/home.html

usmg-mk3475-iv-1409r000

Introducing

The Merck Access Program for KEYTRUDA® (pembrolizumab) for Injection



The Merck Access Program may help answer questions about

- Insurance coverage for patients
- Billing and coding information
- Co-pay assistance for eligible patients
- Benefit investigations, prior authorizations, and appeals
- Referrals to the Patient Assistance Program
- Product distribution

You can also request to be contacted by a Field Reimbursement Associate.

KEYTRUDA®
(pembrolizumab) for Injection 50 mg

Two easy ways to learn more about

The Merck Access Program for KEYTRUDA® (pembrolizumab) for Injection

Visit
merckaccessprogram-keytruda.com

A website where you can download resources and find additional information for you and your patients

Call
855-257-3932
Monday through Friday, 8 AM to 8 PM ET

A dedicated representative may be able to

- Research your patient's insurance benefits
- Obtain information on your patient's out-of-pocket costs
- Provide information on co-pay assistance options
- Refer patients to the Patient Assistance Program
- Answer questions about filling out the enrollment form

MERCK

KEYTRUDA® (pembrolizumab) for Injection 50 mg

KEYTRUDA®
(pembrolizumab) for Injection 50 mg

Dear Customer:

Merck Sharp & Dohme Corp. (Merck), a subsidiary of Merck & Co., Inc., is pleased to announce the availability of KEYTRUDA.

KEYTRUDA is supplied as a 50-mg single-use vial.

HOW SUPPLIED	DESCRIPTION	NDC NUMBER	CATALOG PRICE
KEYTRUDA for Injection	Carton containing one 50-mg single-use vial	0006-3029-02	$2158.00

The following miscellaneous HCPCS[a] codes may be used when submitting a claim for KEYTRUDA, depending on payer requirements. Please consult with the applicable payer to understand its specific billing requirements.

HCPCS CODE	DESCRIPTOR
J9999	Please refer to the 2014 Alpha-Numeric HCPCS File for a complete description of the code.
J3590	Please refer to the 2014 Alpha-Numeric HCPCS File for a complete description of the code.
J3490	Please refer to the 2014 Alpha-Numeric HCPCS File for a complete description of the code.
C9399 (for use only on Medicare hospital outpatient claims)	Please refer to the 2014 Alpha-Numeric HCPCS File for a complete description of the code.

[a]HCPCS=Healthcare Common Procedure Coding System. Source: Centers for Medicare & Medicaid Services; Alpha-Numeric HCPCS.

DIMENSION/WEIGHT	CASE QUANTITY	DIMENSION/WEIGHT BY CASE	SHIPPING CASE QUANTITY
2.8″ × 3.3″ × 1.5″ 1.4 oz	1	16.5″ × 3.5″ × 12.0″ approximately 4.0 lbs	36

MERCK

KEYTRUDA®
(pembrolizumab) for Injection 50 mg

The Merck Access Program for KEYTRUDA

The Merck Access Program has been designed to provide information that can help answer questions specific to access and support for KEYTRUDA. The Merck Access Program may answer questions about:

- Insurance coverage for patients
- Billing and coding information
- Co-pay assistance for eligible patients
- Benefit investigations, prior authorizations, and appeals
- Referrals to the Patient Assistance Program
- Product distribution

You can also request to be contacted by a Field Reimbursement Associate.

Distribution of KEYTRUDA

KEYTRUDA is available through authorized distributors. Please contact the Merck Access Program for a list of authorized distributors. Merck does not support the use of any particular distributor, and one is not preferred over the others.

There are 2 easy ways to learn more about the Merck Access Program:
Visit **merckaccessprogram-keytruda.com** for 24-hour access.
Call **855-257-3932** between 8:00 AM and 8:00 PM, Monday through Friday.

If you have any questions regarding KEYTRUDA, please contact your Merck Account Executive.

Sincerely,

Patrick Magri
SVP, Managed Markets and Policy

MERCK

News Release

FOR IMMEDIATE RELEASE

Media Contacts: Ian McConnell (908) 423-3046

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Merck Receives Accelerated Approval of KEYTRUDA® (pembrolizumab), the First FDA-Approved Anti-PD-1 Therapy

WHITEHOUSE STATION, N.J., Sept. 04, 2014 – Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the U.S. Food and Drug Administration (FDA) has approved KEYTRUDA® (pembrolizumab) at a dose of 2 mg/kg every three weeks for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

KEYTRUDA is the first anti-PD-1 (programmed death receptor-1) therapy approved in the United States and received FDA's Breakthrough Therapy designation for advanced melanoma, which was granted based on the significance of early study findings and the unmet medical need. For the recommended 2 mg/kg dose based on data in 89 patients, the overall response rate was 24 percent (95% CI: 15, 34), with one complete response and 20 partial responses (21/89). At the time of analysis, 86 percent (18/21) of patients with objective responses had ongoing responses with durations ranging from 1.4+ to 8.5+ months, including eight patients with ongoing responses of 6 months or longer. Fourteen percent (3/21) had progression of disease 2.8, 2.9, and 8.2 months after initial response.

KEYTRUDA is a humanized monoclonal antibody that works by increasing the ability of the body's immune system to fight advanced melanoma. KEYTRUDA blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, and may affect both tumor cells and healthy cells. Immune-mediated adverse reactions occurred with KEYTRUDA including pneumonitis, colitis, hepatitis, hypophysitis, nephritis, hyperthyroidism, and hypothyroidism. Based on the severity of the adverse reaction, KEYTRUDA should be withheld or discontinued and corticosteroids administered. Based on its mechanism of action, KEYTRUDA may cause fetal harm when administered to a pregnant woman. Female patients of reproductive potential should be advised of the potential hazard to a fetus. For

more information regarding immune-mediated adverse reactions and use in pregnancy, see “Selected Important Safety Information” below.

“KEYTRUDA embodies Merck’s unwavering commitment to pursue breakthrough science to help people who are facing the most challenging diseases,” said Kenneth C. Frazier, chairman and chief executive officer, Merck. “We are grateful to the people with advanced melanoma who participated in our trials, and the scientific and medical community for the shared effort that has led to the accelerated approval of KEYTRUDA.”

“The accelerated FDA approval of KEYTRUDA is a meaningful development for patients with advanced melanoma,” said Dr. Omid Hamid, Director of the Melanoma Center at The Angeles Clinic and Research Institute, and a principal investigator for the pembrolizumab melanoma clinical program. “Our new ability to target the PD-1 pathway with KEYTRUDA is a very exciting step in the immunotherapy field.”

Merck is conducting ongoing Phase 2 and 3 clinical studies in advanced melanoma, which are designed to provide further confirmatory evidence for KEYTRUDA (pembrolizumab) in this indication. Merck plans to make KEYTRUDA available within one week from today’s FDA approval.

Study Cohort Supporting the Accelerated FDA Approval of Single-Agent KEYTRUDA

The approval of KEYTRUDA was based on data from a multi-center, open-label, randomized, dose-comparative study cohort of the ongoing KEYNOTE-001 Phase 1b trial in patients with unresectable or metastatic melanoma and progression of disease. Key eligibility criteria included prior treatment with ipilimumab (two or more doses at 3 mg/kg or higher) and a BRAF or MEK inhibitor, if BRAF V600 mutation positive; and disease progression within 24 weeks following the last dose of ipilimumab. Patients were randomized to receive 2 mg/kg (n=89) or 10 mg/kg (n=84) of KEYTRUDA every 3 weeks until unacceptable toxicity or disease progression. The major efficacy outcome measures were confirmed overall response rate as assessed by blinded independent central review using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and duration of response. Tumor response was assessed every 12 weeks.

Selected Important Safety Information for KEYTRUDA

Pneumonitis occurred in 12 (2.9%) of 411 patients, including Grade 2 or 3 cases in 8 (1.9%) and 1 (0.2%) patients respectively, receiving KEYTRUDA. Monitor patients for signs and symptoms of pneumonitis. Evaluate suspected pneumonitis with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for Grade 2; permanently discontinue KEYTRUDA for Grade 3 or 4 pneumonitis.

Colitis (including microscopic colitis) occurred in 4 (1%) of 411 patients, including Grade 2 or 3 cases in 1 (0.2%) and 2 (0.5%) patients respectively, receiving KEYTRUDA. Monitor patients for signs

and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold KEYTRUDA for Grade 2 or 3; permanently discontinue KEYTRUDA (pembrolizumab) for Grade 4 colitis.

Hepatitis (including autoimmune hepatitis) occurred in 2 (0.5%) of 411 patients, including a Grade 4 case in 1 (0.2%) patient, receiving KEYTRUDA. Monitor patients for changes in liver function. Administer corticosteroids for Grade 2 or greater hepatitis and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA.

Hypophysitis occurred in 2 (0.5%) of 411 patients, including a Grade 2 case in 1 and a Grade 4 case in 1 (0.2% each) patient, receiving KEYTRUDA. Monitor for signs and symptoms of hypophysitis. Administer corticosteroids for Grade 2 or greater hypophysitis. Withhold KEYTRUDA for Grade 2; withhold or discontinue for Grade 3; and permanently discontinue KEYTRUDA for Grade 4 hypophysitis.

Nephritis occurred in 3 (0.7%) patients receiving KEYTRUDA, consisting of one case of Grade 2 autoimmune nephritis (0.2%) and two cases of interstitial nephritis with renal failure (0.5%), one Grade 3 and one Grade 4. Monitor patients for changes in renal function. Administer corticosteroids for Grade 2 or greater nephritis. Withhold KEYTRUDA for Grade 2; permanently discontinue KEYTRUDA for Grade 3 or 4 nephritis.

Hyperthyroidism occurred in 5 (1.2%) of 411 patients, including Grade 2 or 3 cases in 2 (0.5%) and 1 (0.2%) patients respectively, receiving KEYTRUDA. Hypothyroidism occurred in 34 (8.3%) of 411 patients, including a Grade 3 case in 1 (0.2%) patient, receiving KEYTRUDA. Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Administer corticosteroids for Grade 3 or greater hyperthyroidism. Withhold KEYTRUDA for Grade 3; permanently discontinue KEYTRUDA for Grade 4 hyperthyroidism. Isolated hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids.

The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of patients treated with KEYTRUDA: exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, adrenal insufficiency, myasthenic syndrome, optic neuritis, and rhabdomyolysis.

Based on its mechanism of action, KEYTRUDA may cause fetal harm when administered to a pregnant woman. If used during pregnancy, or if the patient becomes pregnant during treatment, apprise the patient of potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose of KEYTRUDA.

KEYTRUDA was discontinued for adverse reactions in 6% of 89 patients who received the recommended dose of 2 mg/kg and 9% of 411 patients across all doses studied. Serious adverse

reactions occurred in 36% of patients receiving KEYTRUDA (pembrolizumab). The most frequent serious adverse drug reactions reported in 2% or more of patients were renal failure, dyspnea, pneumonia, and cellulitis.

The most common adverse reactions (reported in ≥20% of patients) were fatigue (47%), cough (30%), nausea (30%), pruritus (30%), rash (29%), decreased appetite (26%), constipation (21%), arthralgia (20%), and diarrhea (20%).

The recommended dose of KEYTRUDA is 2 mg/kg administered as an intravenous infusion over 30 minutes every three weeks until disease progression or unacceptable toxicity. No formal pharmacokinetic drug interaction studies have been conducted with KEYTRUDA.

It is not known whether KEYTRUDA is excreted in human milk. Because many drugs are excreted in human milk, instruct women to discontinue nursing during treatment with KEYTRUDA. Safety and effectiveness of KEYTRUDA have not been established in pediatric patients.

Commitment to Access for KEYTRUDA

Merck is committed to making KEYTRUDA accessible to patients. Reimbursement support for eligible patients receiving KEYTRUDA, including help with out-of-pocket costs and co-pay assistance, is available through The Merck Access Program. For eligible patients who are uninsured, financial assistance is available through Merck's patient assistance program. More information is available by calling 1-855-257-3932 or visiting www.merckaccessprogram-keytruda.com.

About KEYTRUDA

KEYTRUDA (pembrolizumab) is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. By binding to the PD-1 receptor and blocking the interaction with the receptor ligands, KEYTRUDA releases the PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

Our Focus on Cancer

Our goal is to translate breakthrough science into biomedical innovations to help people with cancer worldwide. For Merck Oncology, helping people fight cancer is our passion, supporting accessibility to our cancer medicines is our commitment, and pursuing research in immuno-oncology is our focus to potentially bring new hope to people with cancer. For more information about our oncology clinical trials, visit www.merck.com/clinicaltrials.

About Merck

Today's Merck is a global healthcare leader working to help the world be well. Merck is known as MSD outside the United States and Canada. Through our prescription medicines, vaccines, biologic

therapies, and consumer care and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to healthcare through far-reaching policies, programs and partnerships. For more information, visit www.merck.com and connect with us on Twitter, Facebook and YouTube.

Forward-Looking Statement

This news release includes "forward-looking statements" within the meaning of the safe harbor provisions of the United States Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of Merck's management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

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

Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in Merck's 2013 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).

# # #

Please see Prescribing Information for KEYTRUDA (pembrolizumab) at http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf and the Medication Guide for KEYTRUDA at http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_mg.pdf.

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