RCN000024741-TH, RCN000024843-TH, RCN000025498-TH, RCN000025779-TH, RCN000025821-TH, RCN000026214-TH, RCN000026180-TH, RCN000026493-TH, RCN000026573-TH

1 PRODUCT NAME

KEYTRUDA®

2. NAME AND STRENGTH OF ACTIVE INGREDIENT (s)

Pembrolizumab 25 mg/ mL

3. PRODUCT DESCRIPTION

Clear to slightly opalescent, colorless to slightly yellow solution.

4. PHARMACODYNAMIC/PHARMACOKINETICS

4.1 Pharmacodynamic Properties

4.1.1 Therapeutic Class

KEYTRUDA (pembrolizumab) is an antineoplastic agent, monoclonal antibody.

4.1.2 Mechanism of Action

PD-1 is an immune-checkpoint receptor that limits the activity of T lymphocytes in peripheral tissues. The PD-1 pathway is an immune control checkpoint that may be engaged by tumor cells to inhibit active T-cell immune surveillance. KEYTRUDA is a high affinity antibody against PD-1, which exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and PD-L2, on antigen presenting or tumor cells. By inhibiting the PD-1 receptor from binding to its ligands, KEYTRUDA reactivates tumor-specific cytotoxic T lymphocytes in the tumor microenvironment and reactivates anti-tumor immunity.

The anti-angiogenic effect of lenvatinib (multi-TKI) in combination with the immune-stimulatory effect of pembrolizumab (anti-PD-1) results in a tumor microenvironment with greater T-cell activation to help overcome primary and acquired resistance to immunotherapy and may improve tumor responses compared to either treatment alone.

In preclinical murine models, PD-1 plus TKI inhibitors have demonstrated enhanced anti-tumor activity compared to either agent alone.

4.1.3 Pharmacodynamics

Based on the modeling of dose/exposure relationships for efficacy and safety for pembrolizumab, there are no clinically significant differences in efficacy and safety between the doses of 200 mg or 2 mg/kg every 3 weeks or 400 mg every 6 weeks.

In peripheral blood of patients who received KEYTRUDA 2 mg/kg every 3 weeks or 10 mg/kg every 2 weeks or 3 weeks, an increased percentage of activated (i.e., HLA-DR+) CD4+ and CD8+ T-cells was observed after treatment at all doses and schedules without an increase in the circulating T-lymphocyte number.

4.2 Pharmacokinetics

The pharmacokinetics of pembrolizumab was studied in 2993 patients with various cancers who received doses in the range of 1 to 10 mg/kg every 2 weeks, 2 to 10 mg/kg every 3 weeks, or 200 mg every 3 weeks. There are no clinically meaningful differences in pharmacokinetics of pembrolizumab across indications.

4.2.1 Absorption

KEYTRUDA is dosed via the IV route and therefore is immediately and completely bioavailable.

4.2.2 Distribution

Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (6.0 L; coefficient of variation [CV]: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

4.2.3 Metabolism

Pembrolizumab is catabolized through non-specific pathways; metabolism does not contribute to its clearance.

4.2.4 Elimination

Pembrolizumab clearance (CV%) is approximately 23% lower [geometric mean, 195 mL/day (40%)] after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%:37%]); this decrease in clearance with time is not considered clinically important. The geometric mean value (CV%) for the terminal half-life ($t_{½}$) is 22 days (32%).

Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration (Cmax), trough concentration (Cmin), 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.

4.2.5 Special Populations

The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The following factors had no clinically important effect on the clearance of pembrolizumab: age (range 15-94 years), gender, race, mild or moderate renal impairment, mild or moderate hepatic impairment, and tumor burden. The relationship between body weight and clearance supports the use of either fixed dose or body weight-based dosing to provide adequate and similar control of exposure. Pembrolizumab concentrations with weight-based dosing at

2 mg/kg every 3 weeks in pediatric patients (2 to 17 years) are comparable to those of adults at the same dose.

Renal Impairment

The effect of renal impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analysis in patients with mild (GFR <90 and ≥60 mL/min/1.73 m^2) or moderate (GFR<60 and ≥30 mL/min/1.73 m^2) renal impairment compared to patients with normal (GFR ≥90 mL/min/1.73 m^2) renal function. No clinically important differences in the clearance of pembrolizumab were found between patients with mild or moderate renal impairment and patients with normal renal function. KEYTRUDA has not been studied in patients with severe (GFR <30 and ≥15 mL/min/1.73 m^2) renal impairment. *[See RECOMMENDED DOSE AND MODE OF ADMINISTRATION (6.4).]*

Hepatic Impairment

The effect of hepatic impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analysis in patients with mild and moderate hepatic impairment (total bilirubin (TB) 1.0 to 1.5 x ULN or AST >ULN and TB >1.5 to 3 x ULN and any AST, respectively, as defined using the National Cancer Institute criteria of hepatic dysfunction) compared to patients with normal hepatic function (TB and AST ≤ULN). No clinically important differences in the clearance of pembrolizumab were found between patients with mild or moderate hepatic impairment and normal hepatic function. KEYTRUDA has not been studied in patients with severe (TB >3 x ULN and any AST) hepatic impairment. *[See RECOMMENDED DOSE AND MODE OF ADMINISTRATION (6.5).]*

5. INDICATIONS

Melanoma

KEYTRUDA™ (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma.

KEYTRUDA is indicated for the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma who have undergone complete resection.

Non-Small Cell Lung Carcinoma

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic non-squamous non-small cell lung carcinoma (NSCLC), with no EGFR or ALK genomic tumor aberrations.

KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.

KEYTRUDA as monotherapy is indicated for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumors express PD-L1 with a ≥1% tumor proportion score (TPS) as determined by a validated test, with no EGFR or ALK genomic tumor aberrations.

KEYTRUDA as monotherapy is indicated for the treatment of patients with advanced NSCLC whose tumors express PD-L1 with a ≥1% TPS as determined by a validated test and who have received platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have received prior therapy for these aberrations prior to receiving KEYTRUDA.

KEYTRUDA is indicated for the treatment of patients with resectable Stage II, IIIA, or IIIB (T3-4N2) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment.

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC who have undergone complete resection.

Head and Neck Cancer

KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC).

KEYTRUDA, as monotherapy, is indicated for the treatment of patients with metastatic or unresectable recurrent HNSCC with disease progression on or after platinum-containing chemotherapy.

Classical Hodgkin Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with relapsed or refractory classical Hodgkin lymphoma (cHL).

Primary Mediastinal B-Cell Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory primary mediastinal B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy.

Urothelial Carcinoma

KEYTRUDA, in combination with enfortumab vedotin, is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.

KEYTRUDA, as monotherapy, is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by a validated test, or in patients who are not eligible for any platinum containing chemotherapy regardless of PD- L1 status.

KEYTRUDA, as monotherapy, is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have received platinum-containing chemotherapy.

KEYTRUDA, as monotherapy, 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.

Gastric Cancer

KEYTRUDA, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma.

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.

Esophageal Cancer

KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the esophagus or gastroesophageal junction.

KEYTRUDA, as monotherapy, is indicated for the treatment of patients with recurrent locally advanced or metastatic esophageal cancer whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by a validated test, and who have received one prior line of systemic therapy.

KEYTRUDA, as monotherapy, is indicated for the treatment of patients with recurrent locally advanced or metastatic esophageal cancer who have received two or more prior lines of systemic therapy.

Microsatellite Instability-High Cancer

KEYTRUDA is indicated for the treatment of adult and pediatric patients with advanced microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancer, as determined by a validated test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Colorectal Cancer

KEYTRUDA is indicated for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by a validated test.

Hepatocellular Carcinoma

KEYTRUDA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with an anti-angiogenic tyrosine kinase inhibitor (TKI) or oxaliplatin-based chemotherapy

Biliary Tract Carcinoma

KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the treatment of patients with locally advanced unresectable or metastatic biliary tract carcinoma (BTC).

Cervical Cancer

KEYTRUDA, in combination with chemoradiotherapy (CRT), is indicated for the treatment of patients with high-risk, locally advanced cervical cancer.

KEYTRUDA, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.

KEYTRUDA, as monotherapy, is indicated for the treatment of patients with recurrent or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by a validated test, with disease progression on or after chemotherapy.

Renal Cell Carcinoma

KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

KEYTRUDA, in combination with lenvatinib, is indicated for the first-line treatment of patients with advanced RCC.

KEYTRUDA, as monotherapy, is indicated for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Endometrial Carcinoma

KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

KEYTRUDA, as monotherapy, is indicated for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by a validated test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

Tumor Mutational Burden-High Cancer

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 a validated test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Triple-Negative Breast Cancer

KEYTRUDA is indicated for the treatment of patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery.

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10) as determined by a validated test.

6. RECOMMENDED DOSE AND MODE OF ADMINISTRATION

6.1 General

Patient Selection

If specified in the indication, select patients for treatment with KEYTRUDA based on the presence of positive PD-L1 expression, MSI-H or dMMR tumor status, or TMB-H tumor status [see INDICATIONS (5)].

PD-L1 expression should be evaluated using the PD-L1 IHC 22C3 pharmDx™ kit or equivalent. For gastric cancer, in patients treated with two or more prior lines of therapy, if PD-L1 expression is not detected in an archival specimen, obtain a tumor biopsy for PD-L1 testing, if feasible.

MSI or MMR tumor status should be evaluated using a validated test.

TMB-H tumor status should be evaluated using the FoundationOne® CDx assay or equivalent.

Because subclonal dMMR mutations and microsatellite instability may arise in high grade gliomas during temozolomide therapy, it is recommended to test for TMB-H, MSI-H, and dMMR in the primary tumor specimens obtained prior to initiation of temozolomide chemotherapy in patients with high- grade gliomas.

Recommended Dosing

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults with head and neck cancer, cHL, PMBCL, urothelial carcinoma, gastric cancer, MSI-H cancer, esophageal cancer, HCC, RCC, cervical cancer, endometrial carcinoma, colorectal cancer, TMB-H cancer, TNBC, previously untreated NSCLC or for adjuvant treatment of melanoma is either:

- 200 mg every 3 weeks or
- 400 mg every 6 weeks.

The recommended dose of KEYTRUDA in adults with melanoma or previously treated NSCLC is 2 mg/kg every 3 weeks.

For use in combination, see the prescribing information for the concomitant therapies. When administering KEYTRUDA as part of a combination with intravenous chemotherapy, KEYTRUDA should be administered first.

For urothelial carcinoma patients treated with KEYTRUDA in combination with enfortumab vedotin, administer KEYTRUDA after enfortumab vedotin when given on the same day.

For urothelial carcinoma patients treated with KEYTRUDA in combination with enfortumab vedotin, the recommended initial dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) as an intravenous solution on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity.

For RCC patients treated with KEYTRUDA in combination with axitinib, see the prescribing information regarding dosing of axitinib. When used in combination with KEYTRUDA, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer.

For endometrial carcinoma and RCC patients treated with KEYTRUDA in combination with lenvatinib, the recommended initial dose of lenvatinib is 20 mg orally once daily until disease progression or unacceptable toxicity.

Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity. Atypical responses (i.e., an initial transient increase in tumor size or small new lesions within the first few months followed by tumor shrinkage) have been observed. Clinically stable patients with initial evidence of disease progression should remain on treatment until disease progression is confirmed.

For the adjuvant treatment of melanoma, NSCLC, or RCC, KEYTRUDA should be administered for up to one year or until disease recurrence or unacceptable toxicity.

For the neoadjuvant and adjuvant treatment of resectable NSCLC, patients should be treated with neoadjuvant KEYTRUDA in combination with chemotherapy for 12 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for 39 weeks or until disease recurrence or unacceptable toxicity.

For the neoadjuvant and adjuvant treatment of high-risk early-stage TNBC, patients should be treated with neoadjuvant KEYTRUDA in combination with chemotherapy for 8 doses of 200 mg every 3 weeks or 4 doses of 400 mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for 9 doses of 200 mg every 3 weeks or 5 doses of 400 mg every 6 weeks or until disease recurrence or unacceptable toxicity. Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity related to KEYTRUDA as neoadjuvant treatment in combination with chemotherapy should not receive KEYTRUDA monotherapy as adjuvant treatment.

Dose Modifications

No dose reductions of KEYTRUDA are recommended. Withhold or discontinue KEYTRUDA to manage adverse reactions as described in Table 1.

Table 1: Recommended Dose Modifications [see Warnings and Precautions (8)]

Adverse reactions	Severity	Dose modification
Immune mediated pneumonitis	Moderate (Grade 2)	Withhold until adverse reactions recover to Grades 0-1*
	Severe or life-threatening (Grades 3 or 4) or recurrent moderate (Grade 2)	Permanently discontinue
Immune mediated colitis	Moderate or severe (Grades 2 or 3)	Withhold until adverse reactions recover to Grades 0-1*
	Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue
Immune mediated nephritis	Moderate (Grade 2)	Withhold until adverse reactions recover to Grades 0-1*
	Severe or life-threatening (Grades 3 or 4)	Permanently discontinue
Immune mediated endocrinopathies	Severe or life-threatening (Grades 3 or 4)	Withhold until adverse reactions recover to Grades 0-1* For patients with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that improves to Grade 2 or lower and is controlled with hormone replacement, continuation of KEYTRUDA may be considered
Immune mediated hepatitis/ non-HCC For liver enzyme elevations in RCC patients treated with combination therapy with axitinib, see	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 to 5 times upper limit of normal (ULN) or total bilirubin >1.5 to 3 times ULN	Withhold until adverse reactions recover to Grades 0-1*
	AST or ALT >5 times ULN or total bilirubin >3 times ULN	Permanently discontinue

Adverse reactions	Severity	Dose modification
dosing guidelines following this table	For patients with liver metastases who begin treatment with moderate (Grade 2) elevation of AST or ALT, if AST or ALT increases ≥50% relative to baseline and lasts ≥1 week	Permanently discontinue
Immune-mediated hepatitis/HCC	AST or ALT with baseline <2 times ULN and increases to ≥5 times ULN; AST or ALT with baseline ≥2 times ULN and increases to >3 times baseline; or AST or ALT >500 U/L regardless of baseline levels Total bilirubin with baseline levels <1.5 mg/dL and increases to >2 mg/dL; total bilirubin with baseline levels ≥1.5 mg/dL and increases to ≥2 times baseline; or total bilirubin >3.0 mg/dL regardless of baseline levels	Withhold until adverse reactions recover to Grades 0-1*
	ALT >20 times ULN; Child Pugh score ≥9 points; gastrointestinal bleeding suggestive of portal hypertension; ascites; or encephalopathy	Permanently discontinue
Immune-mediated skin reactions or Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Severe skin reactions (Grade 3) or suspected SJS or TEN	Withhold until adverse reactions recover to Grades 0-1*
	Severe skin reactions (Grade 4) or confirmed SJS or TEN	Permanently discontinue
Other immune-mediated adverse reactions	Based on severity and type of reaction (Grade 2 or Grade 3)	Withhold until adverse reactions recover to Grades 0-1*
	Severe or life-threatening (Grades 3 or 4) myocarditis, encephalitis, or Guillain-Barré syndrome	Permanently discontinue
	Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue
Infusion-related reactions	Severe or life-threatening (Grades 3 or 4)	Permanently discontinue

Note: toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v.4)

* If corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks or a treatment-related toxicity does not resolve to Grades 0-1 within 12 weeks after last dose of KEYTRUDA, then KEYTRUDA should be permanently discontinued.

In patients with cHL or PMBCL, with Grade 4 hematological toxicity, KEYTRUDA should be withheld until adverse reactions recover to Grades 0-1.

In patients with RCC being treated with KEYTRUDA in combination with axitinib:

- If ALT or AST ≥3 times ULN but <10 times ULN without concurrent total bilirubin ≥2 times ULN, withhold both KEYTRUDA and axitinib until these adverse reactions recover to Grades 0-1. Consider corticosteroid therapy. 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.
- If ALT or AST ≥10 times ULN or >3 times ULN with concurrent total bilirubin ≥2 times ULN, permanently discontinue both KEYTRUDA and axitinib and consider corticosteroid therapy.

When administering KEYTRUDA in combination with lenvatinib, interrupt one or both or dose reduce or discontinue lenvatinib to manage adverse reactions as appropriate. No dose reductions are recommended for KEYTRUDA.

For recommendations for management of adverse reactions of lenvatinib, refer to the prescribing information for lenvatinib. Recommended dose reductions for lenvatinib when used to treat RCC or endometrial carcinoma are shown in Table 2. For information on median dose and median duration of exposure of lenvatinib in RCC see Section 12 *[See UNDESIRABLE EFFECTS (12)]*.

Table 2: Recommended Dose Reductions of Lenvatinib for Adverse Reactions

Indication	Starting Dose	First Dose Reduction To	Second Dose Reduction To	Third Dose Reduction To
RCC	20 mg orally once daily	14 mg once daily	10 mg once daily	8 mg once daily
Endometrial Carcinoma	20 mg orally once daily	14 mg once daily	10 mg once daily	8 mg once daily

Lenvatinib Dose Modifications for Severe Renal Impairment

The recommended dosage of lenvatinib for patients with RCC or endometrial carcinoma and severe renal impairment (creatinine clearance less than 30 mL/min calculated by Cockcroft-Gault equation using actual body weight) is 10 mg orally once daily. For additional information regarding renal toxicity with lenvatinib, refer to the prescribing information for lenvatinib.

Lenvatinib Dose Modifications for Severe Hepatic Impairment

The recommended dosage of lenvatinib for patients with RCC or endometrial carcinoma and severe hepatic impairment (Child-Pugh C) is 10 mg orally once daily. For additional information regarding hepatotoxicity with lenvatinib, refer to the prescribing information for lenvatinib.

Preparation and Administration

- Protect from light. Do not freeze. Do not shake.
- Equilibrate the vial of KEYTRUDA to room temperature.
- Prior to dilution, the vial of liquid can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. KEYTRUDA is a clear to slightly opalescent, colorless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 4 mL (100 mg) of KEYTRUDA and transfer into an intravenous bag containing 0.9% sodium chloride or 5% glucose (dextrose) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Mix diluted solution by gentle inversion.
- Do not freeze the infusion solution.
- The product does not contain preservative. The diluted product should be used immediately. If not used immediately, diluted solutions of KEYTRUDA may be stored at room temperature for a cumulative time of up to 6 hours. Diluted solutions of KEYTRUDA may also be stored under refrigeration at 2°C to 8°C; however, the total time from dilution of KEYTRUDA to completion of infusion should not exceed 96 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.
- Translucent to white proteinaceous particles may be seen in the diluted solution. Administer infusion solution intravenously over 30 minutes using a sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.
- Discard any unused portion left in the vial.

6.2 Pediatric Patients

For melanoma, cHL, PMBCL, MSI-H or dMMR cancer, and TMB-H cancer, 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.

6.3 Geriatric Patients

No overall differences in safety or efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years). No dose adjustment is necessary in this population.

6.4 Renal Impairment

No dose adjustment is needed for patients with mild or moderate renal impairment. KEYTRUDA has not been studied in patients with severe renal impairment.

6.5 Hepatic Impairment

No dose adjustment is needed for patients with mild or moderate hepatic impairment. KEYTRUDA has not been studied in patients with severe hepatic impairment.

Mode of administration

For intravenous infusion only.

7. CONTRAINDICATIONS

None.

8. WARNINGS AND PRECAUTIONS

Immune-mediated adverse reactions

Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving KEYTRUDA. Immune-mediated adverse reactions can occur after discontinuation of treatment. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of KEYTRUDA, administration of corticosteroids and/or supportive care. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

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 consider administration of corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Restart KEYTRUDA if the adverse reaction remains at Grade 1 or less following corticosteroid taper. If another episode of a severe adverse reaction occurs, permanently discontinue KEYTRUDA. *[See RECOMMENDED DOSE AND MODE OF ADMINISTRATION (6.1) and UNDESIRABLE EFFECTS (12.1).]*

Immune-mediated pneumonitis

Pneumonitis (including fatal cases) has been reported in patients receiving KEYTRUDA *[see UNDESIRABLE EFFECTS (12.1).]*. Monitor patients for signs and symptoms of pneumonitis. If pneumonitis is suspected, evaluate with radiographic imaging and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3), life-threatening (Grade 4) or recurrent moderate

Grade 2) pneumonitis. *[See RECOMMENDED DOSE AND MODE OF ADMINISTRATION (6.1) and Immune-mediated adverse reactions above.]*

Immune-mediated colitis

Colitis has been reported in patients receiving KEYTRUDA *[see UNDESIRABLE EFFECTS (12.1)]*. Monitor patients for signs and symptoms of colitis and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis. *[See RECOMMENDED DOSE AND MODE OF ADMINISTRATION (6.1) and Immune-mediated adverse reactions above.]*

Immune-mediated hepatitis

Hepatitis has been reported in patients receiving KEYTRUDA *[see UNDESIRABLE EFFECTS (12.1)]*. Monitor patients for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis and exclude other causes. Administer corticosteroids (initial dose of 0.5-1 mg/kg/day [for Grade 2 events] and 1-2 mg/kg/day [for Grade 3 or greater events] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA. *[See RECOMMENDED DOSE AND MODE OF ADMINISTRATION (6.1) and Immune-mediated adverse reactions above.]*

Immune-mediated nephritis

Nephritis has been reported in patients receiving KEYTRUDA *[see UNDESIRABLE EFFECTS (12.1)]*. Monitor patients for changes in renal function and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2), and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) nephritis. *[See RECOMMENDED DOSE AND MODE OF ADMINISTRATION (6.1) and Immune-mediated adverse reactions above.]*

Immune-mediated endocrinopathies

Adrenal insufficiency (primary and secondary) has been reported in patients receiving KEYTRUDA. Hypophysitis has also been reported in patients receiving KEYTRUDA *[See UNDESIRABLE EFFECTS (12.1)]*. Monitor patients for signs and symptoms of adrenal insufficiency and hypophysitis (including hypopituitarism) and exclude other causes. Administer corticosteroids to treat adrenal insufficiency and other hormone replacement as clinically indicated, withhold KEYTRUDA for moderate (Grade 2), withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency or hypophysitis. *[See RECOMMENDED DOSE AND MODE OF ADMINISTRATION (6.1) and Immune-mediated adverse reactions above.]*

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving KEYTRUDA *[see UNDESIRABLE EFFECTS (12.1)]*. Monitor patients for hyperglycemia or other signs

and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA in cases of severe hyperglycemia until metabolic control is achieved.

Thyroid disorders, including hyperthyroidism, hypothyroidism and thyroiditis, have been reported in patients receiving KEYTRUDA and can occur at any time during treatment; therefore, monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically. Withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism. *[See RECOMMENDED DOSE AND MODE OF ADMINISTRATION (6.1), UNDESIRABLE EFFECTS (12.1), and Immune-mediated adverse reactions above.]*

For patients with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that improves to Grade 2 or lower and is controlled with hormone replacement, continuation of KEYTRUDA may be considered.

Severe skin reactions

Immune-mediated severe skin reactions have been reported in patients treated with KEYTRUDA. Monitor patients for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids *[See RECOMMENDED DOSE AND MODE OF ADMINISTRATION (6.1)]*.

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients treated with KEYTRUDA. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA. *[See RECOMMENDED DOSE AND MODE OF ADMINISTRATION (6.1)].*

Other immune-mediated adverse reactions

The following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients treated with KEYTRUDA in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010: uveitis, myositis, Guillain-Barré syndrome, pancreatitis encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis (including exacerbation), myelitis, vasculitis, hypoparathyroidism, gastritis and hemolytic anemia. The following were reported in other clinical studies with KEYTRUDA or in postmarketing use: myocarditis, sclerosing cholangitis, and exocrine pancreatic insufficiency.

Cases of these immune-mediated adverse reactions, some of which were severe, have been reported in clinical trials or in postmarketing use.

Transplant-related adverse reactions

Solid organ transplant rejection has been reported in the postmarketing setting in patients treated with KEYTRUDA. Treatment with KEYTRUDA may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment with KEYTRUDA versus the risk of possible organ rejection in these patients.

Acute graft-versus-host-disease (GVHD), including fatal GVHD, after treatment with KEYTRUDA has been reported in patients with a history of allogeneic hematopoietic stem cell transplant (HSCT). Patients who experienced GVHD after their transplant procedure may be at increased risk for GVHD after treatment with KEYTRUDA. Consider the benefit of treatment with KEYTRUDA versus the risk of possible GVHD in patients with a history of allogeneic HSCT.

Elevated liver enzymes when KEYTRUDA is given in combination with axitinib for RCC

When KEYTRUDA is given with axitinib, higher than expected frequencies of Grades 3 and 4 ALT and AST elevations have been reported in patients with advanced RCC [see UNDESIRABLE EFFECTS (12.1)]. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used in monotherapy. Follow medical management guidelines for both drugs. [See RECOMMENDED DOSE AND MODE OF ADMINISTRATION (6.1) and the prescribing information for axitinib.]

Increased mortality in patients with multiple myeloma when KEYTRUDA is added to a thalidomide analogue and dexamethasone

In two randomized clinical trials in patients with multiple myeloma, the addition of KEYTRUDA to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Infusion-related reactions

Severe infusion reactions, including hypersensitivity and anaphylaxis, have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010. For severe infusion reactions, stop infusion and permanently discontinue KEYTRUDA *[see RECOMMENDED DOSE AND MODE OF ADMINISTRATION (6.1)]*. Patients with mild or moderate infusion reaction may continue to receive KEYTRUDA with close monitoring; premedication with antipyretic and antihistamine may be considered.

9. INTERACTIONS WITH OTHER MEDICAMENTS

No formal pharmacokinetic drug interaction studies have been conducted with KEYTRUDA. Since pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

The use of systemic corticosteroids or immunosuppressants before starting KEYTRUDA should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of KEYTRUDA. However, systemic corticosteroids or other immunosuppressants can be used after starting KEYTRUDA to treat immune-mediated adverse reactions. *[See WARNINGS AND PRECAUTIONS (8).]* Corticosteroids can also be used as premedication, when KEYTRUDA is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

10. USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

There are no data on the use of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab; however, 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. These results indicate a potential risk, based on its mechanism of action, that administration of KEYTRUDA during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth. Human IgG4 (immunoglobulin) is known to cross the placental barrier and pembrolizumab is an IgG4; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. KEYTRUDA is not recommended during pregnancy unless the clinical benefit outweighs the potential risk to the fetus. Women of childbearing potential should use effective contraception during treatment with KEYTRUDA and for at least 4 months after the last dose of KEYTRUDA.

10.2 Nursing Mothers

It is unknown whether KEYTRUDA is secreted in human milk. Because many drugs are secreted in human milk, a decision should be made whether to discontinue breast-feeding or to discontinue KEYTRUDA, taking into account the benefit of breast-feeding for the child and the benefit of KEYTRUDA therapy for the woman.

10.3 Pediatric Use

In KEYNOTE-051, 173 pediatric patients (65 children ages 6 months to less than 12 years and 108 adolescents ages 12 years to 17 years) with advanced melanoma, lymphoma, or PD-L1 positive advanced, relapsed, or refractory solid tumors were administered KEYTRUDA 2 mg/kg every 3 weeks. Patients received KEYTRUDA for a median of 4 doses (range 1- 52 doses), with 147 patients (85%) receiving KEYTRUDA for 2 doses or more. The concentrations of pembrolizumab in pediatric patients were comparable to those observed in adult patients at the same dose regimen of 2 mg/kg every 3 weeks.

The safety profile in these pediatric patients was similar to that seen in adults treated with pembrolizumab. The most common adverse reactions (reported in at least 20% of pediatric patients) were pyrexia, vomiting, headache, abdominal pain, anemia, and cough.

Efficacy for pediatric patients with melanoma, cHL, PMBCL, MSI-H or dMMR cancer, or TMB-H cancer is extrapolated from the results in the respective adult populations and supported by data from KEYNOTE-051.

11. PREGNANCY AND LACTATION

Please see **10.1 Pregnancy** and **10.2 Nursing Mothers**

12. UNDESIRABLE EFFECTS

12.1 Clinical Trials Experience

The safety of KEYTRUDA was evaluated in 2799 patients in controlled and uncontrolled studies. The median treatment duration was 4.2 months (range 1 day to 30.4 months) including 1153 patients treated for greater than or equal to six months and 600 patients treated for greater than or equal to one year. KEYTRUDA was discontinued for treatment-related adverse reactions in 5% of patients. Treatment-related serious adverse events (SAEs) reported up to 90 days after the last dose occurred in 10% of patients receiving KEYTRUDA. Of these treatment-related SAEs, the most common were pneumonitis, colitis, diarrhea, and pyrexia.

Immune-mediated adverse reactions ***[see WARNINGS AND PRECAUTIONS (8)]:***

Immune-mediated adverse reactions are presented based on 2799 patients with melanoma and NSCLC. The safety profile was generally similar for patients with melanoma and NSCLC. Table 3 presents the incidence of immune-mediated adverse reactions by Grade that occurred in patients receiving KEYTRUDA.

Table 3: Immune-Mediated Adverse Reactions

	KEYTRUDA 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks n=2799				
Adverse Reaction	All Grades (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
Hypothyroidism *	8.5	6.2	0.1	0	0
Hyperthyroidism†	3.4	0.8	0.1	0	0
Pneumonitis ‡	3.4	1.3	0.9	0.3	0.1
Colitis	1.7	0.4	1.1	<0.1	0
Adrenal Insufficiency	0.8	0.3	0.3	<0.1	0
Hepatitis	0.7	0.1	0.4	<0.1	0
Hypophysitis	0.6	0.2	0.3	<0.1	0
Nephritis §	0.3	0.1	0.1	<0.1	0
Type 1 Diabetes Mellitus	0.2	<0.1	0.1	0.1	0

* In individual studies of patients with HNSCC treated with KEYTRUDA as monotherapy (n=909) the incidence of hypothyroidism was 16.1% (all Grades) with 0.3% Grade 3. In patients with HNSCC treated with KEYTRUDA in combination with platinum and 5-FU chemotherapy (n=276) the incidence of hypothyroidism was 15.2%, all of which were Grades 1 or 2. In patients with cHL (n=389) the incidence of hypothyroidism was 17%, all of which were Grade 1 or 2. In the adjuvant study of patients with resected RCC treated with KEYTRUDA as monotherapy (n=488) the incidence of hypothyroidism was 21% (all Grades) with 0.2% Grade 3.

† In the adjuvant study of patients with resected RCC treated with KEYTRUDA as monotherapy (n=488) the incidence of hyperthyroidism was 12% (all Grades) with 0.2% Grade 3.

‡ In individual studies of patients with NSCLC treated with KEYTRUDA as monotherapy (total n=2602), the incidence of pneumonitis (all Grades) ranged from 3.8% to 8.3%. In cHL patients treated with KEYTRUDA as monotherapy, the incidence of pneumonitis (all Grades) ranged from 5.2% to 10.8% for cHL patients in KEYNOTE-087 (n=210) and KEYNOTE-204 (n=148), respectively.

§ In patients with non-squamous NSCLC treated with KEYTRUDA 200 mg in combination with pemetrexed and platinum chemotherapy (n=405) the incidence of nephritis was 1.7% (all Grades) with 1.0% Grade 3 and 0.5% Grade 4.

Endocrinopathies: The median time to onset of adrenal insufficiency was 5.3 months (range 26 days to 16.6 months). The median duration was not reached (range 4 days to 1.9+ years). Adrenal insufficiency led to discontinuation of KEYTRUDA in 1 (<0.1%) patient. Adrenal insufficiency resolved in 5 patients. The median time to onset of hypophysitis was 3.7 months (range 1 day to 11.9 months). The median duration was 4.7 months (range 8+ days to 12.7+ months). Hypophysitis led to discontinuation of KEYTRUDA in 4 (0.1%) patients. Hypophysitis resolved in 7 patients. The median time to onset of hyperthyroidism was 1.4 months (range 1 day to 21.9 months). The median duration was 2.1 months

(range 3 days to 15.0+ months). Hyperthyroidism led to discontinuation of KEYTRUDA in 2 (<0.1%) patients. Hyperthyroidism resolved in 71 patients. The median time to onset of hypothyroidism was 3.5 months (range 1 day to 18.9 months). The median duration was not reached (range 2 days to 27.7+ months). One (<0.1%) patient discontinued KEYTRUDA due to hypothyroidism.

Pneumonitis: The median time to onset of pneumonitis was 3.3 months (range 2 days to 19.3 months). The median duration was 1.5 months (range 1 day to 17.2+ months). Pneumonitis led to discontinuation of KEYTRUDA in 36 (1.3%) patients. Pneumonitis resolved in 55 patients.

Colitis: The median time to onset of colitis was 3.5 months (range 10 days to 16.2 months). The median duration was 1.3 months (range 1 day to 8.7+ months). Colitis led to discontinuation of KEYTRUDA in 15 (0.5%) patients. Colitis resolved in 41 patients.

Hepatitis: The median time to onset of hepatitis was 1.3 months (range 8 days to 21.4 months). The median duration was 1.8 months (range 8 days to 20.9+ months). Hepatitis led to discontinuation of KEYTRUDA in 6 (0.2%) patients. Hepatitis resolved in 15 patients.

Nephritis: The median time to onset of nephritis was 5.1 months (range 12 days to 12.8 months). The median duration was 3.3 months (range 12 days to 8.9+ months). Nephritis led to discontinuation of KEYTRUDA in 3 (0.1%) patients. Nephritis resolved in 5 patients.

Other adverse events

Melanoma

Table 4 summarizes the adverse events that occurred in at least 10% of patients with melanoma treated with KEYTRUDA in KEYNOTE-006. The most common adverse events (reported in at least 15% of patients) were arthralgia and cough.

Table 4: Adverse Events Occurring in ≥10% of Patients Treated with KEYTRUDA and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grade 3]) (KEYNOTE-006)

	KEYTRUDA 10 mg/kg every 2 or 3 weeks n=555		Ipilimumab 3 mg/kg every 3 weeks n=256	
Adverse Events	**All Grades (%)**	**Grade 3* (%)**	**All Grades (%)**	**Grade 3* (%)**
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	18	0	10	1
Back pain	12	1	7	1
Respiratory, Thoracic and Mediastinal Disorders				
Cough	17	0	7	0
Skin And Subcutaneous Tissue Disorders				
Vitiligo	11	0	2	0

* Of these ≥10% adverse events, none was reported as Grade 4.

Table 5 summarizes the adverse events that occurred in at least 10% of patients with melanoma treated with KEYTRUDA at a dose of 2 mg/kg in KEYNOTE-002. The most common adverse event (reported in at least 20% of patients) was pruritus.

Table 5: Adverse Events Occurring in ≥10% of Patients with Melanoma Treated with KEYTRUDA and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-002)

	KEYTRUDA 2 mg/kg every 3 weeks n=178		Chemotherapy n=171	
Adverse Event	**All Grades (%)**	**Grades 3-4* (%)**	**All Grades (%)**	**Grades 3-4* (%)**
Gastrointestinal Disorders				
Abdominal pain	13	2	8	1
Skin And Subcutaneous Tissue Disorders				
Pruritus	25	0	8	0
Rash	13	0	8	0
Metabolism and Nutrition Disorders				
Hyponatremia	11	3	5	1
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	15	1	10	1

* Of these ≥10% adverse events, none was reported as Grade 4 in patients receiving KEYTRUDA at 2 mg/kg. Hyponatremia was reported as Grade 4 in one patient receiving chemotherapy.

Overall, the safety profile was similar across all doses and between patients previously treated with ipilimumab and patients naïve to treatment with ipilimumab.

Resected Melanoma

Among the 969 patients with resected melanoma enrolled in KEYNOTE 716 and 1019 patients with resected melanoma enrolled in KEYNOTE-054, the adverse reactions were generally similar to those occurring in patients with unresectable or metastatic melanoma or NSCLC.

Non-Small Cell Lung Carcinoma

Combination Therapy

Table 6 summarizes the adverse events that occurred in at least 20% of patients treated with KEYTRUDA, pemetrexed, and platinum chemotherapy in KEYNOTE-189. Adverse events occurring in previously untreated patients with NSCLC receiving KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel in KEYNOTE-407 were generally similar to those occurring in patients in KEYNOTE-189 with the exception of alopecia (46%) and arthralgia (21%).

Table 6: Adverse Events Occurring in ≥20% of Patients Receiving KEYTRUDA with Pemetrexed and Platinum Chemotherapy and at a Higher Incidence than in Patients Receiving Placebo with Pemetrexed and Platinum Chemotherapy (Between-Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-189)

	KEYTRUDA + Pemetrexed + Platinum Chemotherapy n=405		Placebo + Pemetrexed + Platinum Chemotherapy n=202	
Adverse Events	**All Grades* (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
General Disorders and Administration Site Conditions				
Fatigue	41	6	38	2.5
Asthenia	20	6	24	3.5
Gastrointestinal Disorders				
Diarrhea	31	5	21	3.0
Blood and Lymphatic System Disorders				
Neutropenia	27	16	24	12
Skin and Subcutaneous Tissue Disorders				
Rash	20	1.7	11	1.5

* Graded per NCI CTCAE v4.03

Neoadjuvant and Adjuvant Therapy for Resectable NSCLC

Adverse events occurring in patients with resectable NSCLC receiving KEYTRUDA in combination with platinum-containing chemotherapy, given as neoadjuvant treatment and continued as monotherapy adjuvant treatment in KEYNOTE-671, were generally similar to those occurring in patients in other clinical trials across tumor types receiving KEYTRUDA in combination with chemotherapy.

Monotherapy

Table 7 summarizes the adverse events that occurred in at least 10% of previously untreated patients with NSCLC receiving KEYTRUDA in KEYNOTE-042. The most common adverse events (reported in at least 15% of patients) were dyspnea and cough. Adverse events occurring in previously untreated patients with NSCLC receiving KEYTRUDA in KEYNOTE-024 and previously treated patients in KEYNOTE-010 were generally similar to those occurring in patients in KEYNOTE-042.

Table 7: Adverse Events Occurring in ≥10% of NSCLC Patients Treated with KEYTRUDA and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-5]) (KEYNOTE-042)

	KEYTRUDA 200 mg every 3 weeks n=636		Chemotherapy n=615	
Adverse Event	**All Grades* (%)**	**Grades 3-5 (%)**	**All Grades (%)**	**Grades 3-5 (%)**
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	17	2.0	11	0.8
Cough	16	0.2	11	0.3
Endocrine Disorders				
Hypothyroidism	12	0.2	1.5	0

* Graded per NCI CTCAE v4.03

Adjuvant Therapy for Resected NSCLC

Among the 580 patients with resected NSCLC treated with KEYTRUDA in KEYNOTE 091, the adverse reactions were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as monotherapy with the exception of hypothyroidism (21%) and hyperthyroidism (11%).

Other Cancers

Monotherapy

Adverse events occurring in patients with HNSCC, cHL, PMBCL, urothelial carcinoma, gastric cancer, esophageal cancer, MSI-H or dMMR cancer, CRC, MSI-H or MMR endometrial carcinoma, HCC,

cervical cancer, TMB-H cancer, or adjuvant treatment of RCC were generally similar to those occurring in patients with melanoma or NSCLC.

Combination Therapy

Head and Neck Cancer

In patients with HNSCC receiving KEYTRUDA plus chemotherapy (platinum and 5-FU), adverse events occurring at a greater severity (Grades 3-4) and at a higher incidence (≥2% difference) compared to cetuximab plus chemotherapy (platinum and 5-FU) were: fatigue (7% vs. 4.9%), mucosal inflammation (10% vs. 5%), and stomatitis (8% vs. 3.5%).

Urothelial Carcinoma

In patients with urothelial carcinoma receiving KEYTRUDA plus enfortumab vedotin, adverse events were generally similar to those observed in patients receiving KEYTRUDA or enfortumab vedotin as monotherapy, with the exception of a higher than expected incidence of rash maculo-papular (47% all Grades; 15% Grade 3).

Gastric Cancer

In patients with gastric cancer receiving KEYTRUDA plus chemotherapy (fluoropyrimidine and platinum), adverse events occurring in at least 20% of patients and at a higher incidence (≥2% difference) of Grades 3-4 severity compared to placebo plus chemotherapy (fluoropyrimidine and platinum) were: anemia (12% vs. 10%), platelet count decreased (7% vs. 5%).

In patients with gastric cancer receiving KEYTRUDA plus trastuzumab and chemotherapy (fluoropyrimidine and platinum), adverse events occurring in at least 20% of patients and at a higher incidence (≥2% difference) of Grades 3-4 severity compared to placebo plus trastuzumab and chemotherapy (fluoropyrimidine and platinum) were: vomiting (4.6% vs. 1.9%), anemia (14% vs.12%), decreased platelet count (14% vs.10%), and lymphopenia (13% vs.9%).

Cervical Cancer

In patients with cervical cancer receiving KEYTRUDA plus CRT (cisplatin plus external beam radiation therapy [EBRT] followed by brachytherapy [BT]), adverse events occurring at a higher incidence (≥2% difference) of Grades 3-5 severity for KEYTRUDA plus CRT compared to placebo plus CRT was leukopenia (13% vs. 11%).

In patients with cervical cancer receiving KEYTRUDA plus chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab, adverse events occurring at a higher incidence (≥2% difference) of Grades 3-5 severity for KEYTRUDA plus chemotherapy with or without bevacizumab compared to placebo plus chemotherapy with or without bevacizumab were: anemia (30% vs. 27%), neutropenia (12% vs. 10%), thrombocytopenia (8% vs. 5%), asthenia (3.6% vs. 1.6%).

Esophageal Cancer

In patients with esophageal cancer, adverse events occurring in at least 20% of patients and at a higher incidence (≥2% difference) of Grades 3-5 severity for KEYTRUDA in combination with chemotherapy (cisplatin and 5-FU) compared to placebo plus chemotherapy (cisplatin and 5-FU) were: vomiting (7% vs. 5%), stomatitis (6% vs. 3.8%), neutrophil count decreased (24.1% vs. 17.3%), and white blood cell count decreased (9.2% vs. 4.9%).

Renal Cell Carcinoma

In Combination with Axitinib (KEYNOTE-426)

The most common adverse events that occurred in at least 20% of previously untreated patients with RCC receiving KEYTRUDA and axitinib in KEYNOTE-426 were diarrhea, hypertension, fatigue, hypothyroidism, decreased appetite, palmar-plantar erythrodysaesthesia syndrome, nausea, ALT increased, AST increased, dysphonia, cough and constipation.

In KEYNOTE-426, a higher than expected incidence of Grades 3 and 4 ALT increased (20%) and AST increased (13%) were observed in previously untreated patients with RCC receiving KEYTRUDA in combination with axitinib. The median time to onset of ALT increased was 2.3 months (range: 7 days to 19.8 months). In patients with ALT ≥3 times ULN (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. Of the patients who recovered, 92 (84%) were rechallenged with either KEYTRUDA (3%) or axitinib (31%) monotherapy or with both (50%). Of these patients, 55% had no recurrence of ALT >3 times ULN, and of those patients with recurrence of ALT >3 times ULN, all recovered. There were no Grade 5 hepatic events*. [See RECOMMENDED DOSE AND MODE OF ADMINISTRATION (6.1) and WARNINGS AND PRECAUTIONS (8).]*

In Combination with Lenvatinib (KEYNOTE-581)

Table 8 summarizes the adverse events that occurred in at least 20% of patients treated with KEYTRUDA and lenvatinib in KEYNOTE-581.

Table 8: Adverse Events Occurring in ≥20% of Patients Receiving KEYTRUDA with Lenvatinib and at a Higher Incidence than in Patients Receiving Sunitinib (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-581)

	KEYTRUDA + lenvatinib n=352		Sunitinib n=340	
Adverse Events	**All Grades* (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Gastrointestinal Disorders				
Diarrhea	61	10	49	5
Nausea	36	2.6	33	0.6
Vomiting	26	3.4	20	1.5

	KEYTRUDA + lenvatinib n=352		Sunitinib n=340	
Adverse Events	**All Grades* (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Constipation	25	0.9	19	0
Abdominal pain	21	2.0	8	0.9
Vascular Disorders				
Hypertension	55	28	41	19
Endocrine Disorders				
Hypothyroidism	47	1.4	26	0
Metabolism and Nutrition Disorders				
Decreased appetite	40	4.0	31	1.5
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	30	0	4.1	0
Investigations				
Decreased weight	30	8	9	0.3
Renal and Urinary Disorders				
Proteinuria	30	8	13	2.9
Skin and Subcutaneous Tissue Disorders				
Rash	27	3.7	14	0.6
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	28	1.4	15	0.3
Nervous System Disorders				
Headache	23	0.6	16	0.9

* Graded per NCI CTCAE v4.03

Endometrial Carcinoma

Table 9 summarizes the adverse events that occurred in at least 20% of patients treated with KEYTRUDA and lenvatinib in KEYNOTE-775. Adverse events occurring in patients with endometrial carcinoma receiving KEYTRUDA in combination with lenvatinib in KEYNOTE-146 were generally similar to those occurring in patients in KEYNOTE-775.

Table 9: Adverse Events Occurring in ≥20% of Patients Receiving KEYTRUDA with Lenvatinib and at a Higher Incidence than in Patients Receiving Doxorubicin or Paclitaxel (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-775)

	KEYTRUDA + lenvatinib n=406		Doxorubicin or paclitaxel n=388	
Adverse Events*	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Vascular Disorders				
Hypertension	64	37.9	5.2	2.3
Endocrine Disorders				
Hypothyroidism	57	1.2	0.8	0
Gastrointestinal Disorders				
Diarrhea	54	8‡	20	2.1
Nausea	50	3.4	46	1.3
Vomiting	37	2.7	21	2.3
Abdominal pain	20	2.5	14	1.3
Metabolism and Nutrition Disorders				
Decreased appetite	45	8‡	21	0.5
Investigations				
Decreased weight	34	10	6	0.3
Increased ALT	21	4.6	5	0.8
General Disorders and Administration Site Conditions				
Fatigue	33	5	28	3.1
Asthenia	24	6	24	3.9
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	31	1.7	8	0
Renal and Urinary Disorders				
Proteinuria	29	5	2.8	0.3
Infections				
Urinary tract infection	26	3.9	10	1.0
Nervous System Disorders				
Headache	25	0.5	9	0.3
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	23	0	0.5	0
Skin and Subcutaneous Tissue Disorders				

	KEYTRUDA + lenvatinib n=406		Doxorubicin or paclitaxel n=388	
Adverse Events*	**All Grades† (%)**	**Grades 3-4 (%)**	**All Grades† (%)**	**Grades 3-4 (%)**
Palmar-plantar erythrodysaesthesia syndrome	21	2.7	0.8	0

* The median duration of study treatment was 7.6 months (range: 1 day to 26.8 months). The median duration of exposure to KEYTRUDA was 6.9 months (range: 1 day to 25.8 months) compared to 3.4 months (range: 1 day to 25.8 months) for chemotherapy.
† Graded per NCI CTCAE v4.03
‡ There was one Grade 5 (0.2%) reported.

Discontinuation of KEYTRUDA, lenvatinib or both due to an adverse event (Grades 1-4) occurred in 30% of patients; 15% KEYTRUDA, and 11% both drugs. The most common adverse events leading to discontinuation of KEYTRUDA were diarrhea, increased ALT, and intestinal obstruction (each 1.0%). Refer to the lenvatinib prescribing information for lenvatinib discontinuation information.

Dose interruptions of KEYTRUDA, lenvatinib, or both due to an adverse event occurred in 69% of patients; KEYTRUDA was interrupted in 50%, and both drugs were interrupted in 31% of patients. The most common adverse events leading to interruption of KEYTRUDA (≥2%) were diarrhea (8%), increased ALT (3.9%), hypertension (3.4%), increased AST (3.2%), decreased appetite (2.2%), fatigue (2.2%), urinary tract infection (2.2%), proteinuria (2.0%), and asthenia (2.0%). Refer to the lenvatinib prescribing information for lenvatinib interruption information.

Triple-Negative Breast Cancer

KEYNOTE-522: Controlled study of neoadjuvant and adjuvant treatment of patients with high-risk early-stage TNBC.

In patients with high-risk early-stage TNBC receiving KEYTRUDA in combination with chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide), given as a neoadjuvant treatment and continued as monotherapy adjuvant treatment, adverse events occurring in at least 20% of the patients and at a higher incidence (≥5% difference) compared to patients with TNBC receiving placebo in combination with chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide), given as a neoadjuvant treatment and continued alone as adjuvant treatment were diarrhea (41% vs. 34%), rash (30% vs. 24%), pyrexia (28% vs. 19%), and decreased appetite (23% vs. 17%). Of these adverse events, Grades 3-4 events were diarrhea (3.2% vs. 1.8%), rash (1.8% vs. 0.3%), pyrexia (1.3% vs. 0.3%), and decreased appetite (0.9% vs. 0.3%).

KEYNOTE-355: Controlled study of combination therapy in patients with locally recurrent unresectable or metastatic TNBC

In patients with TNBC receiving KEYTRUDA in combination with chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin), adverse events occurring in at least 20% of the patients and at a higher incidence (≥5% difference) compared to patients with TNBC receiving placebo in combination with chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin) were diarrhea (28% vs. 23%), decreased appetite (21% vs. 14%), and rash (20% vs. 12%). Of these adverse events, Grades 3-4 events were diarrhea (1.8% vs. 1.8%), decreased appetite (0.8% vs. 0.4%), and rash (0.8% vs. 0.0%).

Biliary Tract Carcinoma

In patients with BTC receiving KEYTRUDA plus chemotherapy (gemcitabine and cisplatin), adverse events occurring at a higher incidence (≥5%) compared to placebo plus chemotherapy were pyrexia (26% vs. 20%), rash (17% vs. 9%), pruritus (15% vs. 10%) and hypothyroidism (9% vs. 2.6%). Of these adverse events, Grades 3-4 events were pyrexia (2.3% vs. 0.9%), rash (0.6% vs. 0.4%), pruritus (0.0% vs. 0.0%) and hypothyroidism (0.2% vs 0.0%).

12.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of KEYTRUDA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Musculoskeletal and connective tissue disorders: arthritis
Eye disorders: Vogt-Koyanagi-Harada syndrome
Immune system disorders: hemophagocytic lymphohistiocytosis
Nervous system disorders: optic neuritis

13. OVERDOSE AND TREATMENT

There is no information on overdosage with KEYTRUDA. The maximum tolerated dose of KEYTRUDA has not been determined. In clinical trials, patients received up to 10 mg/kg with a similar safety profile to that seen in patients receiving 2 mg/kg.

In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

14. STORAGE CONDITION

Store in a refrigerator (2°C to 8°C; 36°F to 46°F).
Protect from light. Do not freeze. Do not shake.

For storage conditions after dilution of the medicinal product, *see RECOMMENDED DOSE AND MODE OF ADMINISTRATION (6.1)*.

15. DOSAGE FORMS AND PACKAGING AVAILABLE

Dosage forms: Injection: 100 mg/4 mL (25 mg/mL) solution in a single-use vial

Availability: KEYTRUDA injection (solution): carton containing one 100 mg/4 mL (25 mg/mL), single-use vial

16. NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER

MSD (Thailand) Ltd., Bangkok, Thailand

17. DATE OF RIVISION OF PACKAGE INSERT

November 2023

WARNINGS:

This drug may cause undesirable effects. Must use only under the supervision of a physician. Information on product-specific warnings and precautions and undesirable effects is provided *[see Warnings and precautions (8) and Undesirable effects (12)].*