PRODUCT INFORMATION
KEYTRUDA®
(pembrolizumab)
powder for solution for infusion

NAME OF THE MEDICINE

pembrolizumab

CAS No.: 1374853-91-4

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies
ATC code: Not yet assigned.

DESCRIPTION

One vial contains 50 mg of pembrolizumab.

After reconstitution, 1 mL of solution contains 25 mg of pembrolizumab.

KEYTRUDA (pembrolizumab) is a selective humanized monoclonal antibody designed to block 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. Pembrolizumab is produced in Chinese hamster ovary cells by recombinant DNA technology.

KEYTRUDA is a sterile, preservative-free, white to off-white lyophilized powder. It is reconstituted and diluted for intravenous infusion.

List of excipients

L-histidine
Sucrose
Polysorbate-80

PHARMACOLOGY

Pharmacology and pharmacological actions

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 tumour 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 tumour cells. By inhibiting the PD-1 receptor from binding to its ligands, KEYTRUDA reactivates tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and reactivates anti-tumour immunity.

In peripheral blood of patients with advanced melanoma 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.

Pharmacokinetics

The pharmacokinetics of pembrolizumab were studied in 479 patients with metastatic or unresectable melanoma or carcinoma who received doses in the range of 1 to 10 mg/kg every 2 or 3 weeks.

Absorption

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

Distribution

Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (~7.7 L; CV: 14%). As an antibody, pembrolizumab is not expected to bind to plasma proteins in a specific manner.

Metabolism

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

Elimination

The systemic clearance of pembrolizumab is ~0.2 L/day (CV: 28%) and the terminal half-life ($t_{½}$) is ~26 days (CV: 24%).

Exposure to pembrolizumab as expressed by peak concentration (C_{max}) or area under the plasma concentration time curve (AUC) increased dose proportionally within the dose range for efficacy. Upon repeated dosing, the clearance of pembrolizumab was found to be independent of time, and systemic accumulation was approximately 2.1-fold when administered every 3 weeks. Steady-state concentrations of pembrolizumab were reached by 18 weeks; the mean C_{min} at steady-state was 23 µg/mL during a regimen of 2 mg/kg every 3 weeks.

Special populations

The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The clearance of pembrolizumab increased with increasing body weight; resulting exposure differences are adequately addressed by administration on a mg/kg basis. The following factors had no clinically important effect on the clearance of pembrolizumab: age (range 18-94 years), gender, mild or moderate renal impairment, mild hepatic impairment, and tumour burden. The effect of race could not be assessed due to limited data available in non-Caucasian ethnic groups.

Renal Impairment

The effect of renal impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild (GFR <90 and ≥60 mL/min/1.73 m^2; n=210) or moderate (GFR <60 and ≥30 mL/min/1.73 m^2; n=43) renal impairment compared to patients with normal (GFR ≥90 mL/min/1.73 m^2; n=221) 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 DOSAGE AND ADMINISTRATION]*.

Hepatic Impairment

The effect of hepatic impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild hepatic impairment (total bilirubin (TB) 1.0 to 1.5 x ULN or AST >ULN as defined using the National Cancer Institute criteria of hepatic dysfunction; n=59) compared to patients with normal hepatic function (TB and AST ≤ULN; n=410). No clinically

important differences in the clearance of pembrolizumab were found between patients with mild hepatic impairment and normal hepatic function. KEYTRUDA has not been studied in patients with moderate (TB >1.5 to 3 x ULN and any AST) or severe (TB >3 x ULN and any AST) hepatic impairment *[See DOSAGE AND ADMINISTRATION]*.

CLINICAL TRIALS

Clinical Studies in Unresectable or Metastatic Melanoma

The safety and efficacy of KEYTRUDA were investigated in an uncontrolled, open-label study for the treatment of unresectable or metastatic melanoma. Efficacy was evaluated for 411 patients from three of the defined cohorts of P001 who were previously treated with ipilimumab or naïve to treatment with ipilimumab and received KEYTRUDA at a dose of 2 mg/kg every 3 weeks (n=162), 10 mg/kg every 3 weeks (n=192) or 10 mg/kg every 2 weeks (n=57). The study excluded patients with autoimmune disease; medical conditions that required immunosuppression; 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; medical conditions that required systemic corticosteroids or other immunosuppressive medication; a history of pneumonitis or interstitial lung disease; or any active infection requiring therapy, including HIV, HBV or HCV. Patients were treated with KEYTRUDA until disease progression that was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status, at the discretion of the investigator, based on clinical judgment. Patients were also discontinued if disease progression was confirmed at 4 to 6 weeks with repeat imaging or there was unacceptable toxicity.

Of the 162 patients receiving 2 mg/kg of KEYTRUDA, 57% were male, 35% were ≥65 years of age and the median age was 60 years (range 18-88). All but three patients were white. Seventy-eight percent had M1c stage and 6% of patients had a history of brain metastases. Twenty-two percent of patients received no prior systemic therapy, while 48% had at least two and 20% of patients had three or more prior systemic therapies for advanced melanoma. BRAF mutations were reported in 24% of the study population.

The primary efficacy outcome measure was overall response rate (ORR) as assessed by independent review using confirmed responses and Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Secondary efficacy outcome measures were response duration, disease control rate (DCR), overall survival (OS) and progression free survival (PFS). Tumour response was assessed at 12-week intervals. Overall response is presented in patients who had at least one measurable lesion at baseline by independent review. Objective responses were reported in patients with and without BRAF mutations. See Table 1 for a summary of key efficacy measures in patients previously treated or naïve to treatment with ipilimumab, receiving KEYTRUDA at the recommended dose.

Table 1: Response to KEYTRUDA 2 mg/kg every 3 Weeks in Patients with Unresectable or Metastatic Melanoma

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks in patients previously treated with ipilimumab	KEYTRUDA 2 mg/kg every 3 weeks in patients naïve to treatment with ipilimumab
Best Overall Response*	n=81	n=65
ORR %, (95% CI)	26% (17, 37)	37% (25, 50)
Disease Control % (95% CI)†	51% (39, 62)‡	51% (38, 63)§
Response Duration¶‡	n=21	n=26
Median in weeks (range)	Not reached (6+, 37+)	Not reached (7+, 60+)
% ongoing	86%	92%
PFS#	n=89	n=73
Median in weeks (95% CI)	22 (12, 36)	36 (12, not available)
24-week PFS rate	45%	52%
OS§	n=89	n=73
6-month OS rate	79%	83%

* Based on patients with measurable disease by independent review and RECIST 1.1
† Based on best response of stable disease or better
‡ 1% of patients had a complete response, 25% had a partial response, and 25% had stable disease.
§ 6% of patients had a complete response, 31% had a partial response, and 14% had stable disease.
¶ Based on patients with a confirmed response by independent review
# Based on all treated patients

BRAF mutation status was recorded at baseline. In patients previously treated with ipilimumab who had BRAF wild-type tumours (n=163) or who had BRAF mutant tumours (n=34), the ORR in patients with measurable disease was 31% (95% confidence interval (CI): 24, 39) and 15% (95% CI: 5, 31), respectively, across all doses. All but 5 patients with BRAF mutant tumours received treatment with a BRAF inhibitor before study enrollment. In patients who were naïve to ipilimumab who had BRAF wild-type tumours (n=168), had BRAF mutant tumours but no prior BRAF inhibitor treatment (n=25), or had BRAF mutant tumours and who received prior treatment with a BRAF inhibitor (n=26), the ORR was 43% (95% CI: 34, 53), 37% (95% CI: 18, 58), and 27% (95% CI: 12, 48), respectively.

PD-L1 expression was tested retrospectively by immunohistochemistry research assay with the 22C3 anti-PD-L1 antibody. Of the 275 PD-L1 evaluable patients, 77% were PD-L1 positive (defined as membrane staining of at least 1% of neoplastic or inflammatory cells within the tumour nests). In patients previously treated with ipilimumab who were PD-L1 positive (n=118) and PD-L1 negative (n=23), the ORR in patients with measurable disease was 36% (95% CI: 27, 45) and 9% (95% CI: 1, 28), respectively, across all doses. In patients who were naïve to ipilimumab who were PD-L1 positive (n=76) and PD-L1 negative (n=31), the ORR was 51% (95% CI: 40, 63%) and 10% (95% CI: 2, 26), respectively. The median response duration has not been reached in any PD-L1 subgroup.

Results for patients previously treated with ipilimumab (n=116) and naïve to treatment with ipilimumab (n=76) who received 10 mg/kg of KEYTRUDA every 3 weeks were similar to those seen in patients who received 2 mg/kg of KEYTRUDA every 3 weeks.

Immunogenicity
In clinical studies, one (0.8%) of 130 evaluable patients tested positive for binding antibodies against pembrolizumab during treatment with KEYTRUDA. In this one case, the antibodies were found to be neutralizing against pembrolizumab without apparent clinical sequelae.

In the subgroup of patients treated with the dose regimen of 2 mg/kg every 3 weeks, none of the 97 evaluable patients tested positive for binding antibodies to pembrolizumab during treatment with KEYTRUDA.

INDICATIONS

KEYTRUDA® (pembrolizumab) is indicated as monotherapy for the treatment of unresectable or metastatic melanoma in adults.

CONTRAINDICATIONS

KEYTRUDA is contraindicated in patients with hypersensitivity to pembrolizumab or any of the inactive ingredients *[See DESCRIPTION]*.

PRECAUTIONS

Immune-mediated Adverse Reactions
Immune-mediated adverse reactions occurred in patients receiving KEYTRUDA. In clinical trials, most immune-mediated adverse reactions occurred during treatment, were reversible and managed with interruptions of KEYTRUDA, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of KEYTRUDA.

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 (see below). 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 within 12 weeks after the last dose of KEYTRUDA and with a corticosteroid dose of ≤10 mg prednisone or equivalent per day. If another episode of a severe adverse reaction occurs, permanently discontinue KEYTRUDA *[See DOSAGE AND ADMINISTRATION and ADVERSE EFFECTS]*.

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 P001. 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. If pneumonitis is suspected, evaluate with radiographic imaging and exclude other causes of pneumonitis. 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, ADVERSE EFFECTS and Immune-mediated Adverse Reactions above]*.

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 in P001. 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 and exclude other causes 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, ADVERSE EFFECTS and Immune-mediated Adverse Reactions above]*.

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 P001. 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 (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 for Grade 2 or greater hepatitis and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA *[See DOSAGE AND ADMINISTRATION, ADVERSE EFFECTS and Immune-mediated Adverse Reactions above]*.

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 and exclude other causes of nephritis. Administer corticosteroids for Grade 2 or greater nephritis, withhold KEYTRUDA for moderate (Grade 2), and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) nephritis. *[See DOSAGE AND ADMINISTRATION, ADVERSE EFFECTS and Immune-mediated Adverse Reactions above]*.

Immune-mediated endocrinopathies

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 P001. 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 patients for signs and symptoms of hypophysitis (including hypopituitarism and secondary adrenal insufficiency) and exclude other causes of hypophysitis. Administer corticosteroids, withhold KEYTRUDA for moderate (Grade 2), withhold or discontinue KEYTRUDA for severe (Grade 3) and discontinue for life-threatening (Grade 4) hypophysitis. *[See DOSAGE AND ADMINISTRATION, ADVERSE EFFECTS and Immune-mediated Adverse Reactions above]*.

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving KEYTRUDA. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Exclude other causes of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA in cases of severe hyperglycemia until metabolic control is achieved.

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 P001. 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 P001. 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 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. Treat symptoms of hyperthyroidism as appropriate *[See DOSAGE AND ADMINISTRATION, ADVERSE EFFECTS and Immune-mediated Adverse Reactions above]*. Isolated hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids.

Other immune-mediated adverse events

Across clinical studies with KEYTRUDA in approximately 5000 patients, the following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients: uveitis, myositis and severe skin reactions.

Infusion-related reactions
Across clinical studies with KEYTRUDA in approximately 5000 patients, severe infusion-related reactions have been reported in less than 0.1% of patients. For severe infusion reactions, stop infusion and permanently discontinue KEYTRUDA *[See DOSAGE AND ADMINISTRATION]*. Patients with mild or moderate infusion reaction may continue to receive KEYTRUDA with close monitoring; premedication with antipyretic and antihistamine may be considered.

Patients excluded from clinical trials
Patients with HIV, HBV, HCV, other active infections requiring therapy; and patients with 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. No clinical data is available. Caution should be used in these patient populations.

Patients who experienced less severe adverse reactions (including immune-mediated) on ipilimumab that resolved or improved to Grade 0-1 and ≤10 mg/day prednisone (or equivalent dose) for immune-mediated adverse events. for at least two weeks prior to first dose of KEYTRUDA were included in the clinical trial. Caution should be used in this patient population.

Effects on Fertility
Fertility studies have not been conducted with pembrolizumab. There were no notable effects on male and female reproductive organs observed in general repeat-dose toxicity studies conducted with pembrolizumab in Cynomolgus monkeys, involving IV administration at doses up to 200 mg/kg once a week for 1 month or once every two weeks for 6 months, yielding more than 94 times the exposure in humans at the recommended clinical dose (2 mg/kg every 3 weeks).

Use in Pregnancy (Category D)
There are no data on the use of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab; however, blockade of the PD-1 pathway has been shown in mouse models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. These results indicate that, based on its mechanism of action, a potential risk 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 following the last dose of pembrolizumab.

Use in Lactation
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.

Paediatric Use
Safety and efficacy of KEYTRUDA in children below 18 years of age have not yet been established.

Use in the elderly
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.

Genotoxicity
The genotoxic potential of pembrolizumab has not been evaluated. As a large protein molecule, pembrolizumab is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity
The carcinogenic potential of pembrolizumab has not been evaluated in long-term animal studies.

Effect on Laboratory Tests
Thyroid and liver (hepatic transaminase and bilirubin levels) function tests should be performed at the start of treatment, periodically during treatment and as indicated based on clinical evaluation *[see PRECAUTIONS and DOSAGE AND ADMINISTRATON].*

INTERACTIONS WITH OTHER MEDICINES
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 PRECAUTIONS]*.

ADVERSE EFFECTS
Clinical trials experience
The safety and efficacy of KEYTRUDA were investigated in an uncontrolled, open-label study (three defined cohorts of P001) for the treatment of unresectable or metastatic melanoma. Safety is described for a pooled population of 411 patients (studied across three doses; 2 mg/kg every 3 weeks and 10 mg/kg every 2 or 3 weeks) who were previously treated with ipilimumab (n=221) or naïve to treatment with ipilimumab (n=190). This cohort of P001 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. The average treatment duration was 239 days (range 1-750 days) including 115 patients treated for greater than one year.

KEYTRUDA was discontinued for adverse events in 5% of patients receiving a dose of 2 mg/kg every 3 weeks, and for treatment-related adverse reactions in 3% of patients.

Treatment-related serious adverse events (SAEs) reported up to 90 days after the last dose occurred in 10% of patients receiving KEYTRUDA at a dose of 2 mg/kg every 3 weeks. Of these treatment-related SAEs, those occurring in more than one patient (out of 162) were: hypophysitis (n=2) and colitis (n=2). The most common treatment-related adverse reactions (reported in >10% of patients) included arthralgia (14.8%), diarrhoea (14.8%), fatigue (30.2%), nausea (10%), pruritus (22.8%), cough (11.1%) and rash (19.8%).

Tabulated list of adverse reactions

Treatment-emergent and treatment-related adverse reactions reported in ≥10% of patients with advanced melanoma treated with pembrolizumab 2 mg/kg every 3 weeks (n= 162) are presented in Table 2. These reactions are presented by system organ class and by frequency.

Table 2: Adverse Reactions in ≥10% of Patients with Unresectable or Metastatic Melanoma

	KEYTRUDA 2 mg/kg every 3 weeks (%) n=162	
	Treatment-Emergent	Treatment-Related
Infections and Infestations		
Nasopharyngitis	11	2
Upper respiratory tract infection	11	
Blood and Lymphatic System Disorders		
Anaemia	15	5
Metabolism and Nutrition Disorders		
Decreased appetite	20	9
Psychiatric disorders		
Insomnia	10	
Nervous System Disorders		
Dizziness	10	2
Headache	15	6
Respiratory, Thoracic and Mediastinal Disorders		
Cough	28	10
Dyspnoea	17	7
Gastrointestinal Disorders		
Abdominal pain	12	3
Constipation	20	4
Diarrhoea	27	15
Nausea	30	10
Vomiting	16	6
Skin and Subcutaneous Tissue Disorders		
Pruritus	26	23
Rash	23	20
Vitiligo	10	9
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	23	15
Back pain	12	2
Myalgia	11	6
Pain in extremity	17	2
General Disorders and Administration Site Conditions		
Asthenia	10	6
Fatigue	42	30
Oedema peripheral	14	3
Pyrexia	10	2

Treatment-related adverse reactions that were reported at a frequency ≥5% and ≤10% included: hypothyroidism (9%), erythema (6%), chills (6%).

Laboratory values that worsenend from baseline were reported in the pooled population of 411 patients. Laboratory values that worsened from baseline in ≥ 20% of patients were: increased alanine aminotransferase (23.6%; 1% Grade 3, 0.2% Grade 4), decreased albumin (36.7%; 0.5% Grade 3), increased alkaline phosphatase (22.6%, 0.7% Grade 3), increased aspartate aminotransferase (27.7%, 1.2% Grade 3, 0.5% Grade 4), decreased calcium (28.5%, 0.5% Grade 3, 0.2% Grade 4), cholesterol (23.1%, 0.2% Grade 3), increased glucose (46%, 2.7% Grade 3, 0.5% Grade 4), decreased hemoglobin (51.6%, 4.1% Grade 3, 0.5% Grade 4), decreased

lymphocytes (28.2%, 7.1% Grade 3, 0.2% Grade 4), decreased sodium (32.6%, 5.1% Grade 3), triglycerides (33.3%, 0% Grade 3 or 4).

All studied doses

In 411 patients studied across three doses (2 mg/kg every 3 weeks and 10 mg/kg every 2 or 3 weeks), the pooled safety profile was generally similar to that seen for the subset of patients receiving the recommended dose of 2 mg/kg every 3 weeks. In this pooled dose population, KEYTRUDA was discontinued for treatment-related adverse reactions in 4% of patients and treatment-related serious adverse events (SAEs) reported up to 90 days after the last dose occurred in 9% of patients. Of these treatment-related SAEs, those occurring in more than 1 patient were: hyperthyroidism (n=2), hypophysitis (n=2), colitis (including colitis microscopic) (n=5), nausea (n=2), vomiting (n=2), pyrexia (n=4), dehydration (n=2), confusional state (n=2), renal failure (including acute renal failure) (n=4), dyspnea (n=2) and pneumonitis (n=3).

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

Select potential immune-mediated adverse reactions

Table 3 presents select treatment-related, potential immune-mediated adverse reactions that occurred in patients receiving KEYTRUDA In addition, across clinical studies with KEYTRUDA in approximately 5000 patients, type 1 diabetes mellitus has been reported in 0.1% of patients. *[See DOSAGE AND ADMINISTRATION and PRECAUTIONS]*.

Table 3: Select Treatment-related, Potential Immune-mediated Adverse Reactions

	KEYTRUDA 2 mg/kg every 3 weeks n=162			**KEYTRUDA 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks n=411**		
Adverse Reaction	All Grades (%)	Grade 3 (%)	Grade 4* (%)	All Grades (%)	Grade 3 (%)	Grade 4* (%)
Colitis[†]	1.2	1.2	0	1.0	0.5	0
Hepatitis[‡]	1.2	0	0.6	0.5	0	0.2
Hyperthyroidism	0.6	0	0	1.0	0.2	0
Hypophysitis	1.2	0	0.6	0.5	0	0.2
Hypothyroidism	9.3	0	0	8.3	0.2	0
Nephritis[§]	0	0	0	0.7	0.2	0.2
Pneumonitis	1.2	0.6	0	2.7	0.2	0

* There were no Grade 5 treatment-related potential immune-mediated adverse reactions reported with KEYTRUDA.

† Includes colitis microscopic

‡ Includes autoimmune hepatitis

§ Includes autoimmune nephritis and renal failure with evidence of interstitital nephritis

DOSAGE AND ADMINISTRATION

Treatment must be initiated and supervised by healthcare professionals experienced in the treatment of cancer.

Recommended Dosing

The recommended dose of KEYTRUDA is 2 mg/kg administered intravenously over 30 minutes every 3 weeks. Patients should be treated with KEYTRUDA until disease progression or

unacceptable toxicity. Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. Clinically stable patients with initial evidence of disease progression can under some circumstances remain on treatment until disease progression is confirmed (see CLINICAL TRIALS section for a description of the circumstances where such continued treatment was allowed in the pivotal study).

Dose Modifications

[also see PRECAUTIONS]

Withhold KEYTRUDA for potential immune-mediated adverse reactions including:

- Pneumonitis - moderate (Grade 2; US National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE v.3))
- Colitis - moderate or severe (Grade 2 or 3)
- Symptomatic hypophysitis
- Nephritis - moderate (Grade 2)
- Hyperthyroidism - severe (Grade 3)
- Hepatitis associated with:
    - 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

Resume KEYTRUDA in patients whose adverse reactions recover to Grade 0-1 within 12 weeks after the last dose of KEYTRUDA and with a corticosteroid dose of ≤10 mg prednisone or equivalent per day.

Withhold KEYTRUDA for any other severe or Grade 3 treatment-related adverse reaction.

Permanently discontinue KEYTRUDA:

- If corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day
- If a treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose of KEYTRUDA
- If another episode of any severe toxicity occurs
- For adverse reactions including:
    - Life-threatening (Grade 4) toxicity
    - Potential immune-mediated pneumonitis - severe or life-threatening (Grade 3 or 4)
    - Potential immune-mediated nephritis - severe or life-threatening (Grade 3 or 4)
    - Potential immune-mediated hepatitis associated with:
        - AST or ALT >5 times ULN or total bilirubin >3 times ULN
        - For patients with liver metastasis 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
    - Infusion-related reactions - severe or life-threatening (Grade 3 or 4)

Preparation and Administration

- Prior to reconstitution, the vial of lyophilised powder can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Aseptically add 2.3 mL of sterile water for injection to yield a 25 mg/mL (pH 5.2-5.8) solution of KEYTRUDA.
- To avoid foaming, deliver the water along the walls of the vial and not directly on the lyophilised powder.

- Slowly swirl the vial to allow reconstitution of the lyophilised powder. Allow up to 5 minutes for the bubbles to clear. Do not shake the vials.
  - Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Reconstituted 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 2 mL (50 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 reconstituted and/or diluted product should be used immediately. If not used immediately, reconstituted and diluted solutions of KEYTRUDA solutions may be stored at room temperature for a cumulative time of up to 6 hours. Reconstituted and diluted solutions of KEYTRUDA may also be stored under refrigeration at 2°C to 8°C; however, the total time from reconstitution of KEYTRUDA to completion of infusion should not exceed 24 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.
- 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.
- Product is for single use in one patient only, Discard any residue.

Paediatric Patients
Safety and efficacy of KEYTRUDA in children below 18 years of age have not yet been established.

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.

Renal Insufficiency
No dose adjustment is needed for patients with mild or moderate renal impairment. KEYTRUDA has not been studied in patients with severe renal impairment *[See PHARMACOLOGY].*

Hepatic Insufficiency
No dose adjustment is needed for patients with mild hepatic impairment. KEYTRUDA has not been studied in patients with moderate or severe hepatic impairment *[See PHARMACOLOGY].*

OVERDOSAGE

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.

PRESENTATION AND STORAGE CONDITIONS

Carton of one 50 mg single-use vial

Store in a refrigerator (2°C to 8°C).

For storage conditions after reconstitution or dilution of the medicinal product, *see DOSAGE AND ADMINISTRATION*.

NAME AND ADDRESS OF THE SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
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POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

16 April 2015