ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

KEYTRUDA 50 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 50 mg of pembrolizumab.

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

Pembrolizumab is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody (IgG4/kappa isotype with a stabilising sequence alteration in the Fc region) produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment must be initiated and supervised by specialist physicians experienced in the treatment of cancer.

Posology
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. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Dose delay or discontinuation (see also section 4.4)

Table 1: Guidelines for withholding or discontinuation of KEYTRUDA

Immune-related adverse reactions	**Severity**	**Treatment modification**
Pneumonitis	Grade 2 pneumonitis	Withhold*
	Grade 3 or 4, or recurrent Grade 2 pneumonitis	Permanently discontinue
Colitis	Grade 2 or 3 colitis	Withhold*
	Grade 4 colitis	Permanently discontinue
Nephritis	Grade 2 nephritis with creatinine > 1.5 to 3 times upper limit of normal (ULN)	Withhold*
	Grade ≥ 3 nephritis with creatinine ≥ 3 times ULN	Permanently discontinue
Endocrinopathies	Symptomatic hypophysitis Type 1 diabetes associated with Grade > 3 hyperglycemia (glucose > 250 mg/dL or > 13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥ 3	Withhold* For patients with Grade 3 or Grade 4 endocrinopathy that improved to Grade 2 or lower and is controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued. Hypothyroidism may be managed with replacement therapy without treatment interruption.
Hepatitis	Hepatitis with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN (Grade 2)	Withhold*
	Hepatitis with AST or ALT > 5 times ULN or total bilirubin > 3 times ULN (Grade ≥ 3)	Permanently discontinue
	In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week	Permanently discontinue
Infusion-related reactions	Grade 3 or 4 infusion-related reactions	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).

* until adverse reactions recover to Grade 0-1.

KEYTRUDA should be permanently discontinued:

- For Grade 4 toxicity except for endocrinopathies that are controlled with replacement hormones
- If corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks
- If a treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose of KEYTRUDA
- If any event occurs a second time at Grade ≥ 3 severity.

Patients treated with KEYTRUDA must be given the Patient Alert Card and be informed about the risks of KEYTRUDA (see also package leaflet).

Special populations
Elderly
No overall differences in safety or efficacy were reported between elderly patients (≥ 65 years) and younger patients (< 65 years). No dose adjustment is necessary in this population.

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 (see section 5.2).

Hepatic impairment
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 section 5.2).

Ocular melanoma
There are limited data on the safety and efficacy of KEYTRUDA in patients with ocular melanoma (see section 5.1).

Paediatric population
The safety and efficacy of KEYTRUDA in children below 18 years of age have not yet been established. No data are available.

Method of administration
KEYTRUDA should be administered by intravenous infusion over 30 minutes.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Immune-related adverse reactions
Most immune-related adverse reactions occurring during treatment with pembrolizumab were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of pembrolizumab.

For suspected immune-related adverse reactions, adequate evaluation to confirm aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid taper should be initiated and continued 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.

Pembrolizumab may be restarted within 12 weeks after last dose of KEYTRUDA if the adverse reaction remains at Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.

Pembrolizumab must be permanently discontinued for any Grade 3 immune related adverse reaction that recurs and for any Grade 4 immune related adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones (see sections 4.2 and 4.8).

Immune-related pneumonitis
Pneumonitis has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper); pembrolizumab should be withheld for Grade 2 pneumonitis, and permanently discontinued for Grade 3, Grade 4 or recurrent Grade 2 pneumonitis (see section 4.2). In a study involving 550 patients with non-small cell lung carcinoma (NSCLC), a fatal case of pneumonitis has been reported.

Immune-related colitis
Colitis has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for signs and symptoms of colitis, and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper); pembrolizumab should be withheld for Grade 2 or Grade 3 colitis, and permanently discontinued for Grade 4 colitis (see section 4.2). The potential risk of gastrointestinal perforation should be taken into consideration.

Immune-related hepatitis
Hepatitis has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored 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 other causes excluded. Corticosteroids should be administered (initial dose of 0.5-1 mg/kg/day (for Grade 2 events) and 1-2 mg/kg/day (for Grade ≥ 3 events) prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, pembrolizumab should be withheld or discontinued (see section 4.2).

Immune-related nephritis
Nephritis has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for changes in renal function, and other causes of renal dysfunction excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper) and, based on severity of creatinine elevations, pembrolizumab should be withheld for Grade 2, and permanently discontinued for Grade 3 or Grade 4 nephritis (see section 4.2).

Immune-related endocrinopathies
Severe endocrinopathies, including hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis, hypothyroidism, and hyperthyroidism have been observed with pembrolizumab treatment.

Long-term hormone replacement therapy may be necessary in cases of immune-related endocrinopathies.

Hypophysitis has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for signs and symptoms of hypophysitis (including hypopituitarism and secondary adrenal insufficiency) and other causes excluded. Corticosteroids to treat secondary adrenal insufficiency and other hormone replacement should be administered as clinically indicated, and pembrolizumab should be withheld for symptomatic hypophysitis until the event is controlled with hormone replacement. Continuation of pembrolizumab may be considered, after corticosteroid taper, if needed. (see section 4.2). Pituitary function and hormone levels should be monitored to ensure appropriate hormone replacement.

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes. Insulin should be administered for type 1 diabetes, and pembrolizumab should be withheld in cases of Grade 3 hyperglycaemia until metabolic control is achieved (see section 4.2).

Thyroid disorders, including hypothyroidism, hyperthyroidism and thyroiditis, have been reported in patients receiving pembrolizumab and can occur at any time during treatment; therefore, patients

should be monitored 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. Pembrolizumab should be withheld for Grade ≥ 3 until recovery to Grade ≤ 1 hyperthyroidism. For patients with Grade 3 or Grade 4 hyperthyroidism that improved to Grade 2 or lower, continuation of pembrolizumab may be considered, after corticosteroid taper, if needed (see sections 4.2 and 4.8). Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement.

Other immune-related adverse reactions
The following additional clinically significant, immune-related adverse reactions have been reported in patients receiving pembrolizumab: uveitis, arthritis, myositis, pancreatitis, severe skin reactions, myasthenic syndrome, optic neuritis, rhabdomyolysis, haemolytic anaemia, and partial seizures arising in a patient with inflammatory foci in brain parenchyma (see section 4.8).

Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered.

Pembrolizumab may be restarted within 12 weeks after last dose of KEYTRUDA if the adverse reaction remains at Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.

Pembrolizumab must be permanently discontinued for any Grade 3 immune related adverse reaction that recurs and for any Grade 4 immune related adverse reaction toxicity (see sections 4.2 and 4.8).

Infusion-related reactions
Severe infusion-related reactions have been reported in patients receiving pembrolizumab (see section 4.8). For severe infusion reactions, infusion should be stopped and pembrolizumab permanently discontinued (see section 4.2). Patients with mild or moderate infusion reaction may continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.

Patients excluded from clinical trials
The following patients were excluded from clinical trials: patients with HIV, hepatitis B or hepatitis C infection; active systemic autoimmune disease; prior pneumonitis; a history of severe hypersensitivity to another monoclonal antibody; receiving immunosuppressive therapy; and a history of severe immune-related adverse reactions from treatment with ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (> 10 mg/day prednisone or equivalent) for greater than 12 weeks. Patients with active infections were excluded from clinical trials and were required to have their infection treated prior to receiving pembrolizumab. Patients with active infections occurring during treatment with pembrolizumab were managed with appropriate medical therapy. Patients with clinically significant renal (creatinine > 1.5 x ULN) or hepatic abnormalities (bilirubin > 1.5 x ULN, ALT, AST > 2.5 x ULN in the absence of liver metasteses) at baseline were excluded from clinical trials, therefore information is limited in patients with severe renal and moderate to severe hepatic impairment.

After careful consideration of the potential increased risk, pembrolizumab may be used with appropriate medical management in these patients.

Patient Alert Card
All prescribers of KEYTRUDA must be familiar with the Physician Information and Management Guidelines. The prescriber must discuss the risks of KEYTRUDA therapy with the patient. The patient will be provided with the Patient Alert Card with each prescription.

4.5 Interaction with other medicinal products and other forms of interaction

No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab. 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 pembrolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data on the use of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab; however, in murine models of pregnancy blockade of PD-L1 signaling has been shown to disrupt tolerance to the foetus and to result in an increased foetal loss (see section 5.3). These results indicate a potential risk, based on its mechanism of action, that administration of pembrolizumab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth. Human immunoglobulins G4 (IgG4) are 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 foetus. Pembrolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab.

Women of childbearing potential should use effective contraception during treatment with pembrolizumab and for at least 4 months after the last dose of pembrolizumab.

Breast-feeding
It is unknown whether pembrolizumab is secreted in human milk. Since it is known that antibodies can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision should be made whether to discontinue breast-feeding or to discontinue pembrolizumab, taking into account the benefit of breast-feeding for the child and the benefit of pembrolizumab therapy for the woman.

Fertility
No clinical data are available on the possible effects of pembrolizumab on fertility. Although reproductive and developmental toxicity studies have not been conducted with pembrolizumab, there were no notable effects in the male and female reproductive organs in monkeys based on 1-month and 6-month repeat dose toxicity studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Pembrolizumab may have a minor influence on the ability to drive and use machines. Fatigue has been reported following administration of pembrolizumab (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
Pembrolizumab is most commonly associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of pembrolizumab (see "Description of selected adverse reactions" below).

The safety of pembrolizumab has been evaluated in 1012 patients across three doses (2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks) in clinical studies. In this patient population, the most common adverse reactions (> 10%) with pembrolizumab were diarrhoea (15%), nausea (12%), pruritus (25%), rash (25%), arthralgia (13%) and fatigue (33%). The majority of adverse reactions reported were of Grade 1 or 2 severity. The most serious adverse reactions were immune-related adverse reactions and severe infusion-related reactions (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions reported in more than one of 1012 patients with advanced melanoma treated with pembrolizumab in clinical trials are presented in Table 2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions in patients with advanced melanoma treated with pembrolizumab in clinical trials

Infections and Infestations	
Uncommon	diverticulitis, pneumonia, conjunctivitis, herpes zoster, candida infection, influenza, urinary tract infection, oral herpes, nasopharyngitis, folliculitis
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	
Uncommon	tumour pain
Rare	acrochordon, neoplasm swelling
Blood and lymphatic system disorders	
Common	anaemia, thrombocytopenia
Uncommon	neutropenia, lymphopenia, leukopenia, eosinophilia
Rare	immune thrombocytopenic purpura, haemolytic anaemia, pancytopenia
Immune system disorders	
Rare	autoimmune disorder
Endocrine disorders	
Common	hypophysitis*, hyperthyroidism, hypothyroidism
Uncommon	adrenal insufficiency, thyroiditis*
Metabolism and nutrition disorders	
Common	decreased appetite, dehydration
Uncommon	type 1 diabetes mellitus, hyponatraemia, hypokalaemia, hyperglycaemia, hypophosphataemia, hypoalbuminaemia, hypertriglyceridaemia, hypocalcaemia, hypomagnesaemia, hypercholesterolaemia, hypercalcaemia, hyperuricaemia
Psychiatric disorders	
Uncommon	confusional state*, insomnia, anxiety, libido decreased, depression
Rare	affective disorder, agitation, hallucination, trance
Nervous system disorders	
Common	headache, dysgeusia, neuropathy peripheral, dizziness, paraesthesia
Uncommon	hypoaesthesia, lethargy, neuralgia, peripheral sensory neuropathy, hypogeusia, restless legs syndrome, hypotonia, memory impairment, tremor, balance disorder, disturbance in attention, hyperaesthesia, hypersomnia
Rare	brain oedema, encephalopathy, epilepsy, meningitis noninfective, myasthenic syndrome, convulsion, dysarthria, partial seizures, syncope
Eye disorders	
Common	dry eye
Uncommon	uveitis*, eye pain, visual impairment, eye pruritus, vision blurred, lacrimation increased, ocular hyperaemia, eye irritation, eyelash discolouration, photophobia, vitreous floaters
Rare	diplopia, eye disorder, eyelid disorder, macular degeneration, periorbital oedema, photopsia
Ear and labyrinth disorders	
Common	vertigo
Rare	vertigo positional

Cardiac disorders	
Uncommon	pericardial effusion, palpitations
Rare	atrial fibrillation
Vascular disorders	
Common	hot flush
Uncommon	hypotension, flushing, Raynaud's phenomenon
Rare	hypertension, lymphoedema, vasculitis
Respiratory, thoracic and mediastinal disorders	
Common	pneumonitis*, dyspnea, cough
Uncommon	pleuritic pain, dysphonia, wheezing, nasal congestion, oropharyngeal pain, haemoptysis, productive cough, painful respiration, epistaxis, rhinorrhoea, sneezing,
Rare	pleural effusion, respiratory tract congestion
Gastrointestinal disorders	
Very Common	diarrhoea, nausea
Common	colitis*, vomiting, abdominal pain*, constipation, dry mouth, abdominal distention
Uncommon	pancreatitis, dysphagia, oral pain, gastrooesophageal reflux disease, dyspepsia, gastritis, haemorrhoids, tooth disorder, flatulence, gingival pain, stomatitis, cheilitis
Rare	small intestinal perforation, upper gastrointestinal haemorrhage, epigastric discomfort, glossitis, tooth demineralization
Hepatobiliary disorders	
Uncommon	hepatitis*, cholestasis
Skin and subcutaneous tissue disorders	
Very Common	rash*, pruritus*
Common	severe skin reactions*, vitiligo*, dry skin, erythema, eczema, hyperhidrosis*, skin hypopigmentation, alopecia
Uncommon	palmar-plantar erythrodysaesthesia syndrome, psoriasis, dermatitis acneiform, dermatitis, hair colour changes, papule, photosensitivity reaction, skin disorder, skin lesion, skin mass, hair growth abnormal, lichenoid keratosis, skin discolouration, skin hyperpigmentation, erythema nodosum, pigmentation disorder, skin ulcer
Rare	acne, dermatitis contact
Musculoskeletal and connective tissue disorders	
Very Common	arthralgia
Common	myalgia, muscular weakness, musculoskeletal pain*, pain in extremity, back pain, arthritis, muscle spasms, musculoskeletal stiffness
Uncommon	myositis*, joint stiffness, joint swelling, polymyalgia rheumatica, polyarthritis, pain in jaw, bone pain, flank pain, synovitis, neck pain, muscle twitching
Rare	plantar fasciitis, arthropathy, tendon pain, tendonitis, tenosynovitis
Renal and urinary disorders	
Uncommon	nephritis*, renal failure acute, renal failure, renal failure chronic, pollakiuria, dysuria
Rare	urinary incontinence
Reproductive system and breast disorders	
Uncommon	pelvic pain, erectile dysfunction, menorrhagia
Rare	dysmenorrhoea, haematospermia, pruritus genital, scrotal erythema
General disorders and administration site conditions	
Very Common	fatigue
Common	asthenia, pyrexia, mucosal inflammation, oedema peripheral, influenza like illness, chills
Uncommon	generalised oedema, pain, chest pain, inflammation, gait disturbance, chest discomfort, temperature intolerance, malaise, oedema, face oedema, xerosis, feeling hot, thirst

Rare	inflammatory pain, local swelling, localised oedema, injection site reaction, swelling
Investigations	
Common	aspartate aminotransferase increased*, alanine aminotransferase increased*, weight decreased, blood alkaline phosphatase increased
Uncommon	blood creatine phosphokinase increased, gammaglutamyltransferase increased, amylase increased, blood glucose increased, blood creatinine increased, blood bilirubin increased, blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, triiodothyronine increased, blood triglycerides increased, thyroxine decreased, blood cholesterol increased, thyroxine free increased, transaminases increased, weight increased, blood calcium increased
Rare	autoantibody positive, electrocardiogram QT prolonged, activated partial thromboplastin time prolonged, blood testosterone decreased, blood uric acid increased, C-reactive protein increased, eosinophil count increased
Injury, poisoning and procedural complications	
Common	infusion related reaction*

* Terms represent a group of related events that describe a medical condition rather than a single event. Hypophysitis includes hypopituitarism; thyroiditis includes autoimmune thyroiditis; confusional state includes disorientation; uveitis includes iritis and iridocyclitis; pneumonitis includes interstitial lung disease; colitis includes colitis microscopic and enterocolitis; abdominal pain includes abdominal discomfort, abdominal pain upper, and abdominal pain lower; hepatitis includes autoimmune hepatitis; rash includes rash erythmatous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash vesicular; pruritus includes urticaria and pruritus generalised; severe skin reactions include dermatitis exfoliative, erythema multiforme, exfoliative rash, Stevens-Johnson syndrome; and Grade ≥ 3 pruritis, rash, rash generalised, and rash maculo-papular; vitiligo includes skin depigmentation; hyperhidrosis includes night sweats; musculoskeletal pain includes musculoskeletal discomfort; myositis includes myopathy and rhabdomyolysis; nephritis includes nephritis autoimmune and tubulointerstitial nephritis; infusion-related reaction includes drug hypersensitivity, anaphylactic reaction, hypersensitivity and cytokine release syndrome.

Description of selected adverse reactions

Data for the following immune-related adverse reactions are based on patients who received pembrolizumab across three doses (2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks) in clinical studies (see section 5.1). The management guidelines for these adverse reactions are described in section 4.4.

Immune related adverse reactions (see section 4.4)

Immune-related pneumonitis

Pneumonitis occurred in 26 (2.6%) patients, including Grade 2 or 3 cases in 9 (0.9%) and 5 (0.5%) patients, respectively, receiving pembrolizumab. The median time to onset of pneumonitis was 4.3 months (range 2 days to 19.3 months). The median duration was 2.8 months (range 2 days to 15.1 months). Pneumonitis led to discontinuation of pembrolizumab in 8 (0.8%) patients. Pneumonitis resolved in 17 patients. Grade 1 and Grade 3 pneumonitis were ongoing in 8 (0.8%) and 1 (0.1%) patients, respectively.

Immune-related colitis

Colitis occurred in 16 (1.6%) patients, including Grade 2 or 3 cases in 5 (0.5%) and 9 (0.9%) patients, respectively, receiving pembrolizumab. The median time to onset of colitis was 4.2 months (range 10 days to 9.7 months). The median duration was 1.4 months (range 4 days to 7.2 months). Colitis led to discontinuation of pembrolizumab in 6 (0.6%) patients. Colitis resolved in 15 patients.

Immune-related hepatitis

Hepatitis occurred in 8 (0.8%) patients, including Grade 2, 3 or 4 cases in 2 (0.2%), 4 (0.4%) and 1 (0.1%), patients, respectively, receiving pembrolizumab. The median time to onset of hepatitis was 22 days (range 8 days to 21.4 months). The median duration was 1.3 months (range 1.1 weeks to 2.2 months). Hepatitis led to discontinuation of pembrolizumab in 2 (0.2%) patients. Hepatitis resolved in 6 patients.

Immune-related nephritis
Nephritis occurred in 4 (0.4%) patients, including Grade 2, 3 or 4 cases in 2 (0.2%), 1 (0.1%) and 1 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of nephritis was 6.8 months (range 12 days to 12.8 months). The median duration was 1.1 months (range 2.1 weeks to 3.3 months). Nephritis led to discontinuation of pembrolizumab in 1 (0.1%) patient. Nephritis resolved in 3 patients.

Immune-related endocrinopathies
Hypophysitis occurred in 10 (1.0%) patients, including Grade 2, 3, or 4 cases in 4 (0.4%), 3 (0.3%) and 1 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hypophysitis was 1.5 months (range 1 day to 6.5 months). The median duration was 3.4 months (range 0.8 to 12.7 months Hypophysitis led to discontinuation of pembrolizumab in 4 (0.4%) patients. Hypophysitis resolved in 4 patients, 2 with sequelae.

Hyperthyroidism occurred in 24 (2.4%) patients, including Grade 2 or 3 cases in 4 (0.4%) and 2 (0.2%) patients, respectively, receiving pembrolizumab. The median time to onset of hyperthyroidism was 1.4 months (range 1 day to 21.9 months). The median duration was 1.8 months (range 1.4 weeks to 12.8 months). Hyperthyroidism led to discontinuation of pembrolizumab in 2 (0.2%) patients. Hyperthyroidism resolved in 19 (79%) patients.

Hypothyroidism occurred in 75 (7.4%) patients, including a Grade 3 case in 1 (0.1%) patient, receiving pembrolizumab. The median time to onset of hypothyroidism was 3.5 months (range 5 days to 18.9 months). The median duration was 7.9 months (range 6 days to 24.3 months). No patients discontinued pembrolizumab due to hypothyroidism. Hypothyroidism resolved in 9 (12%) patients.

Immunogenicity
In clinical studies in 997 patients treated with pembrolizumab 2 mg/kg every 3 weeks or 10 mg/kg every two or three weeks, one (0.4%) of 268 evaluable patients tested positive for treatment-emergent antibodies to pembrolizumab. In this one case, the antibodies were found to be neutralising against pembrolizumab without apparent clinical sequelae.

In the subgroup of 334 patients treated with pembrolizumab 2 mg/kg every 3 weeks, none of the 220 evaluable patients tested positive for treatment-emergent antibodies to pembrolizumab.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no information on overdose with pembrolizumab.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies. ATC code: L01XC18

Mechanism of action

KEYTRUDA is an antibody which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. KEYTRUDA potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

Clinical efficacy and safety

KEYNOTE-002: Controlled trial in melanoma patients previously-treated with ipilimumab

The safety and efficacy of pembrolizumab were investigated in KEYNOTE-002, a multicentre, controlled study for the treatment of advanced melanoma in patients previously treated with ipilimumab and if BRAF V600 mutation-positive, a BRAF or MEK inhibitor. Patients were randomised (1:1:1) to receive pembrolizumab at a dose of 2 (n=180) or 10 mg/kg (n=181) every 3 weeks or chemotherapy (n=179; including dacarbazine, temozolomide, carboplatin, paclitaxel, or carboplatin+paclitaxel). The study excluded patients with autoimmune disease or those receiving immunosuppression; further exclusion criteria were a history of severe or life-threatening immune-related adverse reactions from treatment with ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (> 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; ongoing adverse reactions ≥ Grade 2 from previous treatment with ipilimumab; previous severe hypersensitivity to other monoclonal antibodies; a history of pneumonitis or interstitial lung disease; HIV, hepatitis B or hepatitis C infection and ECOG PS ≥ 2.

Patients were treated with pembrolizumab until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Assessment of tumour status was performed at 12 weeks, then every 6 weeks through week 48, followed by every 12 weeks thereafter. Patients on chemotherapy who experienced independently verified progression of disease after the first scheduled disease assessment were able to crossover and receive 2 mg/kg or 10 mg/kg of pembrolizumab every 3 weeks in a double blind fashion.

Of the 540 patients in, 61% were male, 43% were ≥ 65 years (median age was 62 years [range 15-89]) and 98% were white. Eighty-two percent had M1c stage, 73% had at least two and 32% of patients had three or more prior systemic therapies for advanced melanoma. Forty-five percent had an ECOG PS of 1, 40% had elevated LDH and 23% had a BRAF mutated tumour.

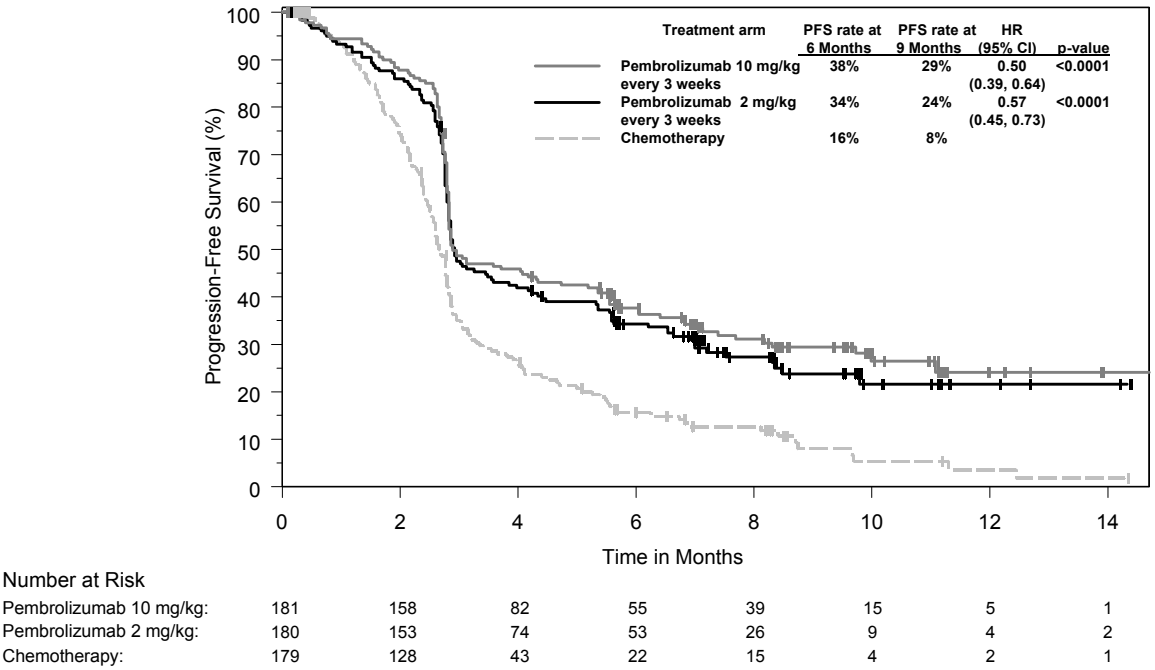
The primary efficacy outcome measures were progression free survival (PFS; as assessed by Integrated Radiology and Oncology Assessment [IRO] review using Response Evaluation Criteria in Solid Tumours [RECIST], version 1.1) and overall survival (OS). Secondary efficacy outcome measures were overall response rate (ORR) and response duration. Table 3 summarises key efficacy measures in patients previously treated with ipilimumab, and the Kaplan-Meier curve for PFS is shown in Figure 1. Both pembrolizumab arms were superior to chemotherapy for PFS, and there was no difference between pembrolizumab doses. OS data were not mature at the time of the PFS analysis. There was no statistically significant difference between pembrolizumab and chemotherapy in the preliminary OS analysis that was not adjusted for the potentially confounding effects of crossover. Of the patients randomised to the chemotherapy arm, 48% crossed over and subsequently received treatment with pembrolizumab.

Table 3: Response to pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks in patients with unresectable or metastatic melanoma in KEYNOTE-002

Endpoint	Pembrolizumab 2 mg/kg every 3 weeks n=180	Pembrolizumab 10 mg/kg every 3 weeks n=181	Chemotherapy n=179
PFS			
Number (%) of patients with event	129 (72%)	126 (70%)	155 (87%)
Hazard ratio* (95% CI)	0.57 (0.45, 0.73)	0.50 (0.39, 0.64)	---
p-Value†	< 0.0001	< 0.0001	---
Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8, 4.7)	2.7 (2.5, 2.8)
OS			
Number (%) of patients with event	73 (41%)	69 (38%)	78 (44%)
Hazard ratio* (95% CI)	0.88 (0.64, 1.22)	0.78 (0.56, 1.08)	---
p-Value†	0.2294	0.0664	---
Best overall response			
ORR % (95% CI)	21% (15, 28)	25% (19, 32)	4% (2, 9)
Complete response %	2%	3%	0%
Partial response %	19%	23%	4%
Response duration			
Median in months (range)	Not reached (1.4+, 11.5+)	Not reached (1.2+, 11.1+)	8.5 (1.6+, 9.5)
% ongoing	87%	80%	63%

* Hazard ratio (pembrolizumab compared to chemotherapy) based on the stratified Cox proportional hazard model
† Based on stratified Log rank test

Figure 1: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-002 (intent to treat population)



KEYNOTE-001: Open label study in melanoma patients naïve and previously-treated with ipilimumab
The safety and efficacy of pembrolizumab for patients with advanced melanoma were investigated in an uncontrolled, open-label study, KEYNOTE-001. Efficacy was evaluated for 276 patients from two defined cohorts, one which included patients previously treated with ipilimumab (and if BRAF V600

mutation-positive, a BRAF or MEK inhibitor) and the other which included patients naïve to treatment with ipilimumab. Patients were randomly assigned to receive pembrolizumab at a dose of 2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks. Patients were treated with pembrolizumab until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Exclusion criteria were similar to those of KEYNOTE-002.

Of the 89 patients receiving 2 mg/kg of pembrolizumab who were previously treated with ipilimumab, 53% were male, 33% were ≥ 65 years of age and the median age was 59 years (range 18-88). All but two patients were white. Eighty-four percent had M1c stage and 8% of patients had a history of brain metastases. Seventy-eight percent had at least two and 35% of patients had three or more prior systemic therapies for advanced melanoma. BRAF mutations were reported in 13% of the study population. All patients with BRAF mutant tumours were previously treated with a BRAF inhibitor.

Of the 51 patients receiving 2 mg/kg of pembrolizumab who were naïve to treatment with ipilimumab, 63% were male, 35% were ≥ 65 years of age and the median age was 60 years (range 35-80). All but one patient was white. Sixty-three percent had M1c stage and 2% of patients had a history of brain metastases. Forty-five percent had no prior therapies for advanced melanoma. BRAF mutations were reported in 20 (39%) patients. Among patients with BRAF mutant tumours, 10 (50%) were previously treated with a BRAF inhibitor.

The primary efficacy outcome measure was ORR as assessed by independent review using RECIST 1.1. Secondary efficacy outcome measures were disease control rate (DCR; including complete response, partial response and stable disease), response duration, PFS and OS. Tumour response was assessed at 12-week intervals. Table 4 summarises key efficacy measures in patients previously treated or naïve to treatment with ipilimumab, receiving pembrolizumab at the recommended dose.

Table 4: Response to pembrolizumab 2 mg/kg every 3 weeks in patients with unresectable or metastatic melanoma in KEYNOTE-001

Endpoint	**Pembrolizumab 2 mg/kg every 3 weeks in patients previously treated with ipilimumab n=89**	**Pembrolizumab 2 mg/kg every 3 weeks in patients naïve to treatment with ipilimumab n=51**
Best Overall Response* by IRO†		
ORR %, (95% CI)	25% (16, 35)	33% (21, 48)
Complete response	3%	10%
Partial response	21%	24%
Disease Control Rate %‡	49%	49%
Response Duration§		
Median in months (range)	Not reached (2.8+, 14.3+)	Not reached (1.6+, 13.8+)
% ongoing	86%¶	82%#
PFS		
Median in months (95% CI)	4.9 (2.8, 8.3)	5.5 (2.8, 14.0)
PFS rate at 6 months	43%	50%
OS		
Median in months (95% CI)	Not reached (11, not available)	Not reached (14, not available)
OS rate at 12 months	60%	72%

* Includes patients without measurable disease at baseline by independent radiology
† IRO = Integrated radiology and oncologist assessment using RECIST 1.1
‡ Based on best response of stable disease or better
§ Based on patients with a confirmed response by independent review, starting from the date the response was first recorded; n=22 for patients previously treated with ipilimumab; n=17 for patients naïve to treatment with ipilimumab
¶ Responders were followed for a minimum of 12 months after initiation of therapy
# Responders were followed for a minimum of 15 months after initiation of therapy

Results for patients previously treated with ipilimumab (n=84) and naïve to treatment with ipilimumab (n=52) who received 10 mg/kg of pembrolizumab every 3 weeks were similar to those seen in patients who received 2 mg/kg of pembrolizumab every 3 weeks.

KEYNOTE-006: Controlled trial in melanoma patients naïve to treatment with ipilimumab
The safety and efficacy of pembrolizumab were investigated in KEYNOTE-006, a multicentre, controlled, Phase III study for the treatment of advanced melanoma in patients who were naïve to ipilimumab. Patients were randomised (1:1:1) to receive pembrolizumab 10 mg/kg every 2 (n=279) or 3 weeks (n=277) or ipilimumab (n=278). Patients with BRAF V600E mutant melanoma were not required to have received prior BRAF inhibitor therapy.

Patients were treated with pembrolizumab until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Assessment of tumour status was performed at 12 weeks, then every 6 weeks through week 48, followed by every 12 weeks thereafter.

Of the 834 patients, 60% were male, 44% were ≥ 65 years (median age was 62 years [range 18-89]) and 98% were white. Sixty-five percent of patients had M1c stage, 9% had a history of brain metastases, 66% had no and 34% had one prior therapy. Thirty-one percent had an ECOG PS of 1, 69% had ECOG PS of 0, and 32% had elevated LDH. BRAF mutations were reported in 302 (36%) patients. Among patients with BRAF mutant tumours, 139 (46%) were previously treated with a BRAF inhibitor.

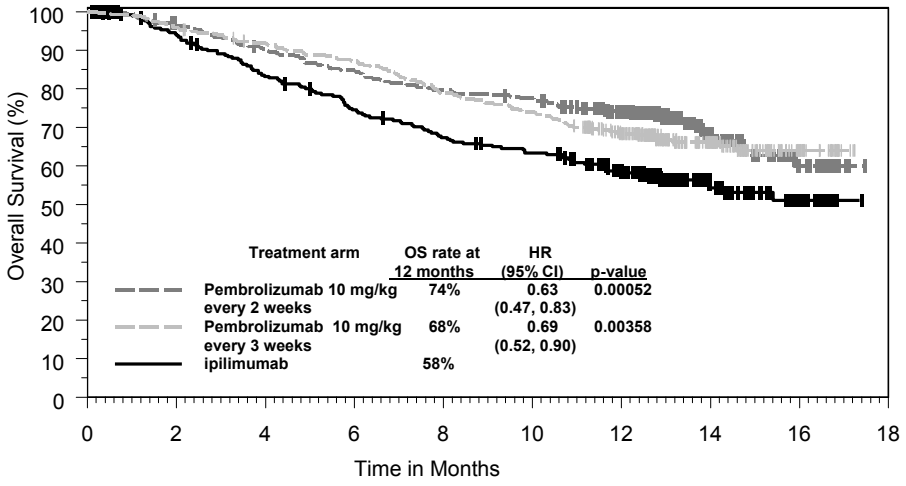
The primary efficacy outcome measures were OS and PFS; as assessed by IRO using RECIST, version 1.1. Table 5 summarises key efficacy measures based on data from an early results report. The Kaplan-Meier curves are shown in Figures 2 and 3.

Table 5: Response to pembrolizumab 10 mg/kg every 2 or 3 weeks in patients with ipilimumab naïve advanced melanoma in KEYNOTE-006*

Endpoint	**Pembrolizumab 10 mg/kg every 3 weeks n=277**	**Pembrolizumab 10 mg/kg every 2 weeks n=279**	**Ipilimumab n=278**
OS			
Number (%) of patients with event	92 (33%)	85 (30%)	112 (40%)
Hazard ratio† (95% CI)	0.69 (0.52, 0.90)	0.63 (0.47, 0.83)	---
p-Value‡	0.00358	0.00052	---
Median in months (95% CI)	Not reached (NA, NA)	Not reached (NA, NA)	Not reached (13, NA)
PFS			
Number (%) of patients with event	157 (57%)	157 (56%)	188 (68%)
Hazard ratio† (95% CI)	0.58 (0.47, 0.72)	0.58 (0.46, 0.72)	---
p-Value‡	< 0.00001	< 0.00001	---
Median in months (95% CI)	4.1 (2.9, 6.9)	5.5 (3.4, 6.9)	2.8 (2.8, 2.9)
Best overall response			
ORR % (95% CI)	33% (27, 39)	34% (28, 40)	12% (8, 16)
Complete response %	6%	5%	1%
Partial response %	27%	29%	10%

* Based on data from an early results report
† Hazard ratio (pembrolizumab compared to ipilimumab) based on the stratified Cox proportional hazard model
‡ Based on stratified Log rank test
NA = not available

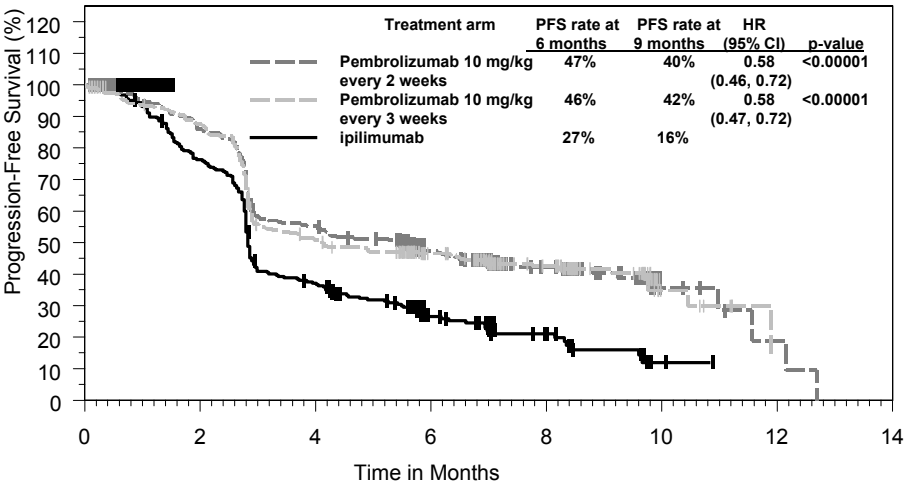
Figure 2: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-006 (intent to treat population)



Number at Risk

Pembrolizumab 10 mg/kg every 2 weeks:	279	266	248	233	219	212	177	67	19	0
Pembrolizumab 10 mg/kg every 3 weeks:	277	266	251	238	215	202	158	71	18	0
ipilimumab:	278	242	212	188	169	157	117	51	17	0

Figure 3: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-006 (intent to treat population)



Number at Risk

Pembrolizumab 10 mg/kg every 2 weeks:	279	231	147	98	49	7	2	0
Pembrolizumab 10 mg/kg every 3 weeks:	277	235	133	95	53	7	1	1
ipilimumab:	278	186	88	42	18	2	0	0

Sub-population analyses

BRAF mutation status

A subgroup analysis of KEYNOTE-002 in patients who were BRAF wild type (n=415; 77%) or BRAF mutant with prior BRAF treatment (n=125; 23%) was performed. The PFS HRs (pooled pembrolizumab [2 mg/kg or 10 mg/kg every 3 weeks] vs. chemotherapy) were 0.51 (95% CI: 0.41, 0.65) for BRAF wild type and 0.56 (95% CI: 0.37, 0.85) for BRAF mutant with prior BRAF treatment. The PFS HRs for pembrolizumab 2 mg/kg every 3 weeks vs. chemotherapy were 0.51 (95% CI: 0.39, 0.67) for BRAF wild type and 0.74 (95% CI: 0.46, 1.18) for BRAF mutant with prior BRAF treatment. The OS HRs for pooled pembrolizumab vs. chemotherapy were 0.83 (95% CI: 0.60, 1.15) for BRAF wild type and 0.82 (95% CI: 0.47, 1.43) for BRAF mutant with prior BRAF treatment. The OS HRs for pembrolizumab 2 mg/kg every 3 weeks vs. chemotherapy were 0.80 (95% CI: 0.55, 1.18) for BRAF wild type and 1.03 (95% CI: 0.55, 1.91) for BRAF mutant with prior BRAF treatment. ORR for pooled pembrolizumab and pembrolizumab 2 mg/kg every 3 weeks

vs. chemotherapy was 27% and 25% vs. 6% for BRAF wild type and 12% and 9% vs. 0% for BRAF mutant with prior BRAF treatment.

A subgroup analysis of KEYNOTE-006 in patients who were BRAF wild type (n=525; 63%), BRAF mutant without prior BRAF treatment (n=163; 20%) and BRAF mutant with prior BRAF treatment (n=139; 17%) was performed. The PFS hazard ratios (HRs) (pooled pembrolizumab [10 mg/kg every 2 or 3 weeks] vs. ipilimumab) were 0.57 (95% CI: 0.45, 0.73) for BRAF wild type, 0.50 (95% CI: 0.32, 0.77) for BRAF mutant without prior BRAF treatment, and 0.73 (95% CI: 0.48, 1.11) for BRAF mutant with prior BRAF treatment. The OS HRs for pooled pembrolizumab vs. ipilimumab were 0.61 (95% CI: 0.46, 0.82) for BRAF wild type, 0.69 (95% CI: 0.33, 1.45) for BRAF mutant without prior BRAF treatment, and 0.75 (95% CI: 0.45, 1.26) for BRAF mutant with prior BRAF treatment. ORR for pooled pembrolizumab vs. ipilimumab was 34% vs. 13% for BRAF wild type, 41% vs. 13% for BRAF mutant without prior BRAF treatment, and 21% vs. 6% for BRAF mutant with prior BRAF treatment.

PD-L1 status

A subgroup analysis of KEYNOTE-002 in patients who were PD-L1 positive (Allred proportion score of ≥ 2 representing PD-L1 membrane expression in ≥ 1% of tumour cells) vs. PD-L1 negative (Allred proportion score of 0 or 1) was performed. PD-L1 expression was tested retrospectively by immunohistochemistry research assay with the 22C3 anti-PD-L1 antibody. Among patients who were evaluable for PD-L1 expression (78%), 69% (n=291) were PD-L1 positive and 31% (n=130) were PD-L1 negative. The PFS HRs (pooled pembrolizumab [2 mg/kg or 10 mg/kg every 3 weeks] vs. chemotherapy) were 0.52 (95% CI: 0.39, 0.68) for PD-L1 positive patients and 0.60 (95% CI: 0.38, 0.94) for PD-L1 negative patients. The PFS HRs for pembrolizumab 2 mg/kg every 3 weeks vs. chemotherapy were 0.54 (95% CI: 0.39, 0.75) for PD-L1 positive patients and 0.89 (95% CI: 0.53, 1.50) for PD-L1 negative patients. The OS HRs for pooled pembrolizumab vs. chemotherapy were 0.82 (95% CI: 0.55, 1.23) for PD-L1 positive patients and 0.77 (95% CI: 0.43, 1.37) for PD-L1 negative patients. The OS HRs for pembrolizumab 2 mg/kg every 3 weeks vs. chemotherapy were 0.93 (95% CI: 0.58, 1.49) for PD-L1 positive patients and 1.19 (95% CI: 0.58, 2.46) for PD-L1 negative patients. ORR for pooled pembrolizumab and pembrolizumab 2 mg/kg every 3 weeks vs. chemotherapy was 26% and 23% vs. 4% for PD-L1 positive patients and 15% and 11% vs. 8% for PD-L1 negative patients.

A subgroup analysis of KEYNOTE-006 in patients who were PD-L1 positive (n=671; 80%) vs. PD-L1 negative (n=150; 18%) was performed. Among patients who were evaluable for PD-L1 expression (98%), 82% were PD-L1 positive and 18% were PD-L1 negative. The PFS HRs (pooled pembrolizumab [10 mg/kg every 2 or 3 weeks] vs. ipilimumab) were 0.53 (95% CI: 0.43, 0.65) for PD-L1 positive patients and 0.73 (95% CI: 0.47, 1.11) for PD-L1 negative patients. The OS HRs for pooled pembrolizumab vs. ipilimumab were 0.56 (95% CI: 0.43, 0.73) for PD-L1 positive patients and 0.95 (95% CI: 0.56, 1.62) for PD-L1 negative patients. The ORRs for the pooled pembrolizumab vs. ipilimumab group were 37% vs. 12% for PD-L1 positive patients and 18% vs. 11% for PD-L1 negative patients.

Ocular melanoma

In 20 subjects with ocular melanoma included in KEYNOTE-001, no objective responses were reported; stable disease was reported in 6 patients.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with pembrolizumab in one or more subsets of the paediatric population in treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of pembrolizumab were studied in 1139 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
Pembrolizumab is dosed via the intravenous 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 (~8.1 L; CV: 22%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

Biotransformation
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: 41%) and the terminal half-life (t½) is ~26 days (CV: 43%).

Linearity/non-linearity
Exposure to pembrolizumab as expressed by peak concentration (Cmax) 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. Near steady-state concentrations of pembrolizumab were achieved by 18 weeks; the mean C_{min} at 18 weeks was approximately 22 mcg/mL at a dose 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 15-94 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 or moderate renal impairment compared to patients with normal 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. Pembrolizumab has not been studied in patients with severe renal impairment.

Hepatic impairment
The effect of hepatic impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild hepatic impairment (as defined using the US National Cancer Institute criteria of hepatic dysfunction) compared to patients with normal hepatic function. No clinically important differences in the clearance of pembrolizumab were found between patients with mild hepatic impairment and normal hepatic function. Pembrolizumab has not been studied in patients with moderate or severe hepatic impairment (see section 4.2).

5.3 Preclinical safety data

The safety of pembrolizumab was evaluated in a 1-month and a 6-month repeat-dose toxicity study in Cynomolgus monkeys administered IV doses of 6, 40 or 200 mg/kg once a week in the 1-month study and once every two weeks in the 6-month study, followed by a 4-month treatment-free period. No findings of toxicological significance were observed and the no observed adverse effect level

(NOAEL) in both studies was ≥ 200 mg/kg, which is 19 times the exposure in humans at the highest clinically tested dose (10 mg/kg).

Animal reproduction studies have not been conducted with pembrolizumab. The PD-1/PD-L1 pathway is thought to be involved in maintaining tolerance to the foetus thoughout pregnancy. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss. These results indicate a potential risk that administration of KEYTRUDA during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine hydrochloride monohydrate
Sucrose
Polysorbate 80

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
18 months

After reconstitution
Chemical and physical in-use stability of the reconstituted and diluted solution has been demonstrated for 24 hours at room temperatures (at or below 25°C). From a microbiological point of view, the product must be used immediately. Do not freeze the reconstituted or diluted solution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and must not be longer than a total of 24 hours. This 24 hour hold may include up to 6 hours at room temperatures (at or below 25°C); any additional hold time must be at 2°C-8°C. If refrigerated, allow the vials and/or intravenous bags to come to room temperature prior to use.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

For storage conditions after reconstitution or dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

15 mL Type I glass vial, with a grey bromobutyl stopper and an aluminium seal with an avocado coloured flip-off cap, containing 50 mg pembrolizumab.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

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 water for injections 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 vial.
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Reconstituted KEYTRUDA is a clear to slightly opalescent, colourless 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 to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Mix diluted solution by gentle inversion.
- Chemical and physical in-use stability of the reconstituted and diluted solution has been demonstrated for 24 hours at room temperatures (at or below 25°C). From a microbiological point of view, the product must be used immediately. Do not freeze the reconstituted or diluted solution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and must not be longer than a total of 24 hours. This 24 hour hold may include up to 6 hours at room temperatures (at or below 25°C); any additional hold time must be at 2°C-8°C. If refrigerated, allow the vials and/or intravenous bags to come to room temperature prior to use. Administer the 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 medicinal products through the same infusion line.
- KEYTRUDA is for single use only. Discard any unused portion left in the vial.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road
Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1024/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

MedImmune, LLC Frederick Manufacturing Center (FMC)
633/636/660 Research Court Frederick
MD 21703-8619, USA

Name and address of the manufacturer responsible for batch release

Schering-Plough Labo NV
Industriepark 30, Heist-op-den-Berg
B-2220, Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch of KEYTRUDA in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing the awareness about the potential:

- immune mediated adverse events
- infusion related reactions

associated with KEYTRUDA use, how to manage them and to enhance the awareness of patients and/or their caregivers on the signs and symptoms relevant to the early recognition/identification of those adverse events.

The MAH shall ensure that in each Member State where KEYTRUDA is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use KEYTRUDA have access to/are provided with the following educational package:

- Physician educational material
- Patient educational material

The physician educational material should contain:

- The Summary of Product Characteristics
- Healthcare Professional FAQ Brochure

The Healthcare Professional FAQ Brochure shall contain the following key elements:
List of important immune-related adverse reactions (irARs) and their symptoms including precautions and treatment, as outlined in section 4.4 of the Summary of Product Characteristics (SmPC):

  - Immune-related hypophysitis (including hypopituitarism and secondary adrenal insufficiency)
  - immune-related pneumonitis
  - Immune-related thyroid disorders (including hypothyroidism and hyperthyroidism)
  - Immune-related uveitis
  - Immune-related colitis
  - Immune-related pancreatitis
  - Immune-related hepatitis
  - Immune-related Type 1 Diabetes Mellitus
  - Immune-related myositis
  - Immune-related nephritis
  - Immune-related severe skin reactions
  - Infusion-related adverse reactions
- Details on how to minimise the safety concerns through appropriate monitoring and management
- Reminder to distribute the Patient Information Brochure and patient alert card

The patient educational material should contain:

- Patient Information Brochure
- The patient alert card

The Patient Information Brochure and Patient alert card shall contain the following key elements:

- Description of the main signs or symptoms of the irARs and the importance of notifying their treating physician immediately if symptoms occur
- The importance of not attempting to self-treat any symptoms without consulting their Healthcare professional first
- The importance of carrying the Patient Alert Card at all times and to show it at all medical visits to healthcare professionals other than the prescriber (e.g. emergency healthcare professionals). The Card reminds patients about key symptoms that need to be reported immediately to the physician/nurse. It also contains prompts to enter contact details of the physician and to alert other physicians that the patient is treated with KEYTRUDA

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
1. Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P002: Randomized, Phase II Study of MK-3475 versus Chemotherapy in Patients with Advanced Melanoma – Final Study Report	1Q 2017
2. Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P006: A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of MK-3475 Compared to Ipilimumab in Patients with Advanced Melanoma – Final Study Report	1Q 2017
3. Post-authorisation efficacy study (PAES): In order to confirm the benefit in BRAF V600 mutant and in PD-L1 negative patient subgroups at the recommended dose, the MAH should provide updated analyses from Study P001 and P002: • Updated efficacy data in subgroups comparing 2 vs 10 mg/kg Q3W from the P002 final analysis. • Efficacy data in subgroups comparing the 2 vs 10 mg/kg Q3W from P001, using the data cut-off date of 18-Oct-2014 from Parts B2 and D of P001 by dose level.	1Q 2017 3Q 2015
4. The value of biomarkers to predict the efficacy of pembrolizumab should be further explored, specifically: Although PD-L1 status is predictive of response in advanced melanoma patients, durable responses have been observed in PD-L1 negative patients. Additional biomarkers other than PD-L1 expression status by IHC (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy should be investigated together with more information regarding the pattern of expression of PD-L1 obtained in the ongoing melanoma studies (P001, P002 and P006): • Comparison between PD-L1 IHC staining in archival tissue vs newly obtained • Comparison of PD-L1 IHC between pre and post treatment tumor tissues • Data on the Nanostring RNA gene signature • IHC staining for PD-L2 • Data on RNA and proteomic serum profiling • Data on Immune cell profiling (peripheral blood)	1Q 2017

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

KEYTRUDA 50 mg powder for concentrate for solution for infusion
pembrolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 50 mg of pembrolizumab. After reconstitution, 1 mL of solution contains 25 mg of pembrolizumab.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose.

4. PHARMACEUTICAL FORM AND CONTENTS

powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
For single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

The reconstituted vials and/or diluted intravenous bags may be stored for a cumulative time of up to 24 hours in a refrigerator (2°C - 8°C).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C).

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp and Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1024/001 (1 vial)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

KEYTRUDA 50 mg powder for concentrate for solution for infusion
pembrolizumab
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

KEYTRUDA 50 mg powder for concentrate for solution for infusion
pembrolizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- It is important that you keep the Alert Card with you during treatment.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What KEYTRUDA is and what it is used for

KEYTRUDA contains the active substance pembrolizumab, a protein that works by helping your immune system fight your cancer.

KEYTRUDA is used in adults to treat a kind of skin cancer called melanoma that has spread or cannot be taken out by surgery.

2. What you need to know before you are given KEYTRUDA

You should not be given KEYTRUDA:
- if you are allergic to pembrolizumab or any of the other ingredients of this medicine (listed in section 6 “Contents of the pack and other information”). Talk to your doctor if you are not sure.

Warnings and precautions
Talk to your doctor or nurse before receiving KEYTRUDA.

Before you get KEYTRUDA, tell your doctor if you:
- have an autoimmune disease (a condition where the body attacks its own cells)
- have pneumonia or inflammation of your lungs (called pneumonitis)
- were previously given ipilimumab, another medicine for treating melanoma, and experienced serious side effects because of that medicine
- had an allergic reaction to other monoclonal antibody therapies
- have or have had chronic viral infection of the liver, including hepatitis B (HBV) or hepatitis C (HCV)
- have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS)
- have liver damage or have had a liver transplant
- have kidney damage or have had a kidney transplant

When you get KEYTRUDA, you can have some serious side effects.
If you have any of the following, call or see your doctor right away. Your doctor may give you other medicines in order to prevent more severe complications and reduce your symptoms. Your doctor may withhold the next dose of KEYTRUDA or stop your treatment with KEYTRUDA.
- inflammation of the lungs: Signs and symptoms may include shortness of breath, chest pain, or coughing
- inflammation of the intestines: Signs and symptoms may include diarrhoea or more bowel movements than usual, black, tarry, sticky stools or stools with blood or mucus, severe stomach pain or tenderness, nausea, vomiting
- inflammation of the liver: Signs and symptoms may include nausea or vomiting, feeling less hungry, pain on the right side of stomach, yellowing of skin or whites of eyes, dark urine, or bleeding or bruising more easily than normal
- inflammation of the kidneys: Signs and symptoms may include changes in the amount or colour of your urine
- inflammation of hormone glands (especially the thyroid, pituitary and adrenal glands): Signs and symptoms may include rapid heartbeat, weight loss, increased sweating, weight gain, hair loss, feeling cold, constipation, deeper voice, muscle aches, dizziness or fainting, headaches that will not go away or unusual headache
- type 1 diabetes: Signs and symptoms may include feeling more hungry or thirsty than usual, need to urinate more often, or weight loss
- inflammation of the eyes: Signs and symptoms may include changes in eyesight
- inflammation in the muscles: Signs and symptoms may include muscle pain or weakness
- inflammation of the pancreas: Signs and symptoms may include abdominal pain, nausea and vomiting
- inflammation of the skin: Signs and symptoms may include rash
- infusion reactions: Signs and symptoms may include shortness of breath, itching or rash, dizziness or fever

Children and adolescents
KEYTRUDA should not to be used in children and adolescents below 18 years of age.

Other medicines and KEYTRUDA
Tell your doctor
- If you are taking other medicines that make your immune system weak. Examples of these may include corticosteroids, such as prednisone. These medicines may interfere with the effect of KEYTRUDA. However, once you are treated with KEYTRUDA, your doctor may give you corticosteroids to reduce the side-effects that you may have with KEYTRUDA.
- If you are taking, have recently taken or might take any other medicines.

Pregnancy
- You must not use KEYTRUDA if you are pregnant unless your doctor specifically recommends it.
- If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor.
- KEYTRUDA can cause harm or death to your unborn baby.
- If you are a woman who could become pregnant, you must use adequate birth control while you are being treated with KEYTRUDA and for at least 4 months after your last dose.

Breast-feeding
- If you are breast-feeding, tell your doctor.
- Do not breast-feed while taking KEYTRUDA.
- It is not known if KEYTRUDA passes into your breast milk.

Driving and using machines
Do not drive or use machines after you have been given KEYTRUDA unless you are sure you are feeling well. Feeling tired or weak is a very common side effect of KEYTRUDA. This can affect your ability to drive or to use machines.

3. How you are given KEYTRUDA

KEYTRUDA will be given to you in a hospital or clinic under the supervision of an experienced doctor.
- Your doctor will give you KEYTRUDA through an infusion into your vein (IV) for about 30 minutes, every 3 weeks.
- Your doctor will decide how many treatments you need.

How much KEYTRUDA will you be given?
The recommended dose is 2 mg of pembrolizumab per kilogram of your body weight.

If you miss an appointment to get KEYTRUDA
- Call your doctor right away to reschedule your appointment.
- It is very important that you do not miss a dose of this medicine.

If you stop receiving KEYTRUDA
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with KEYTRUDA unless you have discussed this with your doctor.
If you have any further questions about your treatment, ask your doctor.

You will also find this information in the Patient Alert Card you have been given by your doctor. It is important that you keep this Alert Card and show it to your partner or caregivers.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When you get KEYTRUDA, you can have some serious side effects. See section 2.

The following side effects have been reported in clinical trials:

Very common (may affect more than 1 in 10 people)
- diarrhoea; nausea
- itching; skin rash
- joint pain
- feeling tired

Common (may affect up to 1 in 10 people)
- decrease in the number of platelets (bruising or bleeding more easily)
- feeling less hungry; weight loss; change in your sense of taste
- dehydration; dry mouth
- headache
- numbness; tingling
- weakness of your hands or feet
- dry eye
- dizziness or spinning sensation
- hot flush
- cough; shortness of breath
- bloating; stomach pain; constipation; vomiting
- hair loss; patches of skin which have lost colour; dry skin; itchy skin; excess sweating
- red raised skin rash, sometimes with blisters, these may include widespread peeling of the skin
- joint pain with swelling; back pain; muscle spasms; muscle weakness, pain, stiffness, aches or tenderness; pain in arms or legs
- unusual tiredness or weakness; chills; flu-like illness; fever

- swelling in the arms or legs
- inflammation of the mucous membranes (e.g., the lining of the mouth or throat)
- decrease in the number of red blood cells
- increased liver enzyme levels in the blood
- inflammation of the lungs or intestines; gland problems including thyroid and pituitary
- reaction related to the infusion of the medicine

Uncommon (may affect up to 1 in 100 people)
- inflammation of the liver, kidneys, pancreas, or the eyes
- type 1 diabetes
- conjunctivitis; shingles; fungal infection; urinary tract infection; herpes of the mouth; infection of the hair roots
- abnormal blood test results
- feeling confused; trouble sleeping; feeling anxious; decreased sex drive; depression
- decreased feeling or sensitivity; decreased feeling in arms or legs; restless legs syndrome; memory impairment; tremor; disturbance in attention; increased sensitivity; numbness, tingling and colour change in fingers and toes when exposed to the cold; temperature intolerance; trouble walking
- eye pain, irritation, itchiness or redness; decreased or blurry eyesight; changes in eyesight; increased tears; eyelash discolouration; uncomfortable sensitivity to light
- fluid around the heart; irregular heartbeat; low blood pressure
- problems with your voice; wheezing; nosebleed; excessive runny nose; sneezing; face swelling
- trouble swallowing; mouth pain; coughing up blood; haemorrhoids; tooth problems; flatulence; mouth ulcers; inflammation of the lips
- blocked bile duct
- redness, swelling, and/or pain on the palms of the hand and/or soles of the feet; acne-like skin problem; hair colour changes; small skin bumps, lumps or sores; increased sensitivity of skin to the sun; thickened, sometimes scaly, skin growth; tender, red bumps under the skin caused by inflammation; changes in hair growth
- tumour pain; bone pain; neck pain; pain in jaw
- kidney failure; difficulty urinating
- pelvic pain; erectile dysfunction; heavy period

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store KEYTRUDA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

Chemical and physical in-use stability of the reconstituted and diluted solution has been demonstrated for 24 hours at room temperatures (at or below 25°C). From a microbiological point of view, the product must be used immediately. Do not freeze the reconstituted or diluted solution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and must not be longer than a total of 24 hours. This 24 hour hold may include up to 6 hours at room temperatures (at or below 25°C); any additional hold time must be at 2°C-8°C.

Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What KEYTRUDA contains
The active substance is pembrolizumab. Each vial contains 50 mg of pembrolizumab.

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

The other ingredients are L-histidine, L-histidine hydrochloride monohydrate, sucrose, and polysorbate 80.

What KEYTRUDA looks like and contents of the pack
KEYTRUDA is a white to off-white lyophilised powder.
It is available in cartons containing one glass vial.

Marketing Authorisation Holder
Merck Sharp & Dohme Limited
Hertford Road
Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

Manufacturer
Schering-Plough Labo NV
Industriepark 30
B-2220 Heist-op-den-Berg
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

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 water for injections 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 vial.
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Reconstituted KEYTRUDA is a clear to slightly opalescent, colourless 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 to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Mix diluted solution by gentle inversion.
- Chemical and physical in use stability of the reconstituted and diluted solution has been demonstrated for 24 hours at room temperatures (at or below 25°C). From a microbiological point of view, the product must be used immediately. Do not freeze the reconstituted or diluted solution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and must not be longer than a total of 24 hours. This 24 hour hold may include up to 6 hours at room temperatures (at or below 25°C); any additional hold time must be at 2°C-8°C. If refrigerated, allow the vials and/or intravenous bags to come to room temperature prior to use. Administer the 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 medicinal products through the same infusion line.
- KEYTRUDA is for single use only. Discard any unused portion left in the vial.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.