Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

UPDATE

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed and 'off label' medicines to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the medicine. This medicine does not yet have a licence (marketing authorisation) for use in patients with metastatic lung cancer who have not been previously treated and are negative for EGFR sensitising mutation and ALK translocation. The information is provided to assist the doctor in prescribing an unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage: http://www.gmc-uk.org/mobile/14327

The scientific opinion is based on the information supplied to the MHRA on the benefits and risks of a promising new medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to licence such a medicine.

The prescribing doctor should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Information for the healthcare professionals

1. NAME OF THE MEDICINAL PRODUCT

Pembrolizumab 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 concentrate 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

Pembrolizumab as monotherapy is indicated for treatment in adults with metastatic non-small cell lung cancer (NSCLC) whose tumours express PD-L1 as determined by a validated test and who have not received prior systemic therapy and are negative for EGFR sensitising mutation and ALK translocation.

4.2 Posology and method of administration

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

PD-L1 testing
Patients should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test (see section 5.1).

Posology
The recommended dose of pembrolizumab is 2 mg/kg administered intravenously over 30 minutes every 3 weeks. Patients should be treated with pembrolizumab 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 pembrolizumab

Immune-related adverse reactions	Severity	Treatment modification
Pneumonitis	Grade 2	Withhold*
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue
Colitis	Grade 2 or 3	Withhold*
	Grade 4	Permanently discontinue
Nephritis	Grade 2 with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN)	Withhold*
	Grade ≥ 3 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	Grade 2 with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN	Withhold*
	Grade ≥ 3 with AST or ALT > 5 times ULN or total bilirubin > 3 times ULN	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	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.

Pembrolizumab 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 pembrolizumab
- If any event occurs a second time at Grade ≥ 3 severity.

Patients treated with pembrolizumab must be given the Patient Alert Card and be informed about the risks of pembrolizumab.

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. Pembrolizumab 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. Pembrolizumab has not been studied in patients with moderate or severe hepatic impairment (see section 5.2).

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

Method of administration
Pembrolizumab 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 pembrolizumab 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
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). Fatal cases of pneumonitis, including interstitial lung disease, have been reported.

Immune-related colitis
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
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
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.

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, Guillain-Barré Syndrome, myasthenic syndrome, 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 pembrolizumab 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
Patients with the following conditions were excluded from clinical trials: active CNS metastases, HIV, hepatitis B or hepatitis C infection; active systemic autoimmune disease; interstitial lung disease; prior pneumonitis requiring systemic corticosteroid therapy; a history of severe hypersensitivity to another monoclonal antibody; receiving immunosuppressive therapy. 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 (bilirubin > 1.5 x ULN, ALT, AST > 2.5 x ULN in the absence of liver metastases) abnormalities 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 pembrolizumab must be familiar with the Physician Information and Management Guidelines. The prescriber must discuss the risks of pembrolizumab therapy with the patient. The patient will be provided with the Patient Alert Card at the time of first administration of pembrolizumab.

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 fetus and to result in an increased fetal 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 fetal harm, including increased rates of abortion or stillbirth. Human immunoglobulins G4 (IgG4) are known to cross the placental barrier; therefore, being an IgG4, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. 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. 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 2,799 patients with advanced melanoma or NSCLC 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 fatigue (24%), rash (19%), pruritus (18%), diarrhoea (12%), nausea (11%) and arthralgia (10%). 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 2,799 patients treated with pembrolizumab in clinical trials are reported 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 treated with pembrolizumab in clinical trials

Blood and lymphatic system disorders	
Common	anaemia
Uncommon	neutropenia, leukopenia, thrombocytopenia, lymphopenia, eosinophilia
Rare	immune thrombocytopenic purpura, haemolytic anaemia
Immune system disorders	
Common	infusion related reaction[a]
Endocrine disorders	
Common	hyperthyroidism, hypothyroidism[b]
Uncommon	hypophysitis[c], adrenal insufficiency, thyroiditis
Metabolism and nutrition disorders	
Common	decreased appetite
Uncommon	type 1 diabetes mellitus[d], hyponatraemia, hypokalaemia, hypocalcaemia
Psychiatric disorders	

Uncommon	insomnia
Nervous system disorders	
Common	headache, dizziness, dysgeusia
Uncommon	epilepsy, lethargy, neuropathy peripheral
Rare	Guillain-Barré syndrome, myasthenic syndrome
Eye disorders	
Common	dry eye
Uncommon	uveitis[e]
Vascular disorders	
Uncommon	hypertension
Respiratory, thoracic and mediastinal disorders	
Common	pneumonitis[f], dyspnea, cough
Gastrointestinal disorders	
Very Common	diarrhoea, nausea
Common	colitis[g], vomiting, abdominal pain[h], constipation, dry mouth
Uncommon	pancreatitis[i]
Rare	small intestinal perforation
Hepatobiliary disorders	
Uncommon	hepatitis[j]
Skin and subcutaneous tissue disorders	
Very Common	rash[k], pruritus[l]
Common	severe skin reactions[m], vitiligo[n], dermatitis acneiform, dry skin, erythema, eczema
Uncommon	lichenoid keratosis[o], psoriasis, alopecia, erythema nodosum, dermatitis, hair colour changes, papule
Musculoskeletal and connective tissue disorders	
Very Common	arthralgia
Common	myositis[p], musculoskeletal pain[q], pain in extremity, arthritis[r]
Uncommon	tenosynovitis[s]
Renal and urinary disorders	
Uncommon	nephritis[t]
General disorders and administration site conditions	
Very Common	fatigue
Common	asthenia, oedema[u], pyrexia, influenza like illness, chills
Investigations	
Common	alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased
Uncommon	amylase increased, blood bilirubin increased, hypercalcaemia

The following terms represent a group of related events that describe a medical condition rather than a single event.

a. infusion-related reactions (drug hypersensitivity, anaphylactic reaction, hypersensitivity and cytokine release syndrome)
b. hypothyroidism (myxoedema)
c. hypophysitis (hypopituitarism)
d. type 1 diabetes mellitus (diabetic ketoacidosis)
e. uveitis (iritis and iridocyclitis)
f. pneumonitis (interstitial lung disease)
g. colitis (colitis microscopic and enterocolitis)
h. abdominal pain (abdominal discomfort, abdominal pain upper and abdominal pain lower)
i. pancreatitis (autoimmune pancreatitis and pancreatitis acute)
j. hepatitis (autoimmune hepatitis and drug induced liver injury)
k. rash (rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular and genital rash)
l. pruritus (urticaria, urticaria papular, pruritus generalized and pruritus genital)

m. severe skin reactions (dermatitis exfoliative, erythema multiforme, exfoliative rash, pemphigoid, Stevens-Johnson syndrome and Grade ≥ 3 of the following: pruritus, rash, rash generalised and rash maculo-papular)
n. vitiligo (skin depigmentation, skin hypopigmentation and hypopigmentation of the eyelid)
o. lichenoid keratosis (lichen planus and lichen sclerosus)
p. myositis (myalgia, myopathy, polymyalgia rheumatica and rhabdomyolysis)
q. musculoskeletal pain (musculoskeletal discomfort, back pain, musculoskeletal stiffness, musculoskeletal chest pain and torticollis)
r. arthritis (joint swelling, polyarthritis and joint effusion)
s. tenosynovitis (tendonitis, synovitis and tendon pain)
t. nephritis (nephritis autoimmune, tubulointerstitial nephritis and renal failure or renal failure acute with evidence of nephritis)
u. oedema (oedema peripheral, generalised oedema, fluid overload, fluid retention, eyelid oedema and lip oedema, face oedema, localized oedema and periorbital oedema)

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. 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 94 (3.4%) patients, including Grade 2, 3, 4 or 5 cases in 36 (1.3%), 25 (0.9%), 7 (0.3%) and 4 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of pneumonitis was 3.3 months (range 2 days to 19.3 months). The median duration was 1.5 months (range 1 day to 17.2+ months). Pneumonitis led to discontinuation of pembrolizumab in 36 (1.3%) patients. Pneumonitis resolved in 55 patients.

Immune-related colitis
Colitis occurred in 48 (1.7%) patients, including Grade 2, 3 or 4 cases in 10 (0.4%), 31 (1.1%) and 2 (<0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of colitis was 3.5 months (range 10 days to 16.2 months). The median duration was 1.3 months (range 1 day to 8.7+ months). Colitis led to discontinuation of pembrolizumab in 15 (0.5%) patients. Colitis resolved in 41 patients.

Immune-related hepatitis
Hepatitis occurred in 19 (0.7%) patients, including Grade 2, 3 or 4 cases in 4 (0.1%), 12 (0.4%) and 2 (<0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hepatitis was 1.3 months (range 8 days to 21.4 months). The median duration was 1.8 months (range 8 days to 20.9+ months). Hepatitis led to discontinuation of pembrolizumab in 6 (0.2%) patients. Hepatitis resolved in 15 patients.

Immune-related nephritis
Nephritis occurred in 9 (0.3%) patients, including Grade 2, 3 or 4 cases in 3 (0.1%), 4 (0.1%) and 1 (<0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of nephritis was 5.1 months (range 12 days to 12.8 months). The median duration was 3.3 months (range 12 days to 8.9+ months). Nephritis led to discontinuation of pembrolizumab in 3 (0.1%) patients. Nephritis resolved in 5 patients.

Immune-related endocrinopathies
Hypophysitis occurred in 17 (0.6%) patients, including Grade 2, 3 or 4 cases in 6 (0.2%), 8 (0.3%) and 1 (<0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hypophysitis was 3.7 months (range 1 day to 11.9 months). The median duration was 4.7 months (range 8+ days to 12.7+ months). Hypophysitis led to discontinuation of pembrolizumab in 4 (0.1%) patients. Hypophysitis resolved in 7 patients, 2 with sequelae.

Hyperthyroidism occurred in 96 (3.4%) patients, including Grade 2 or 3 cases in 22 (0.8%) and 4 (0.1%) 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 2.1 months (range 3 days to 15.0+ months). Hyperthyroidism led to discontinuation of pembrolizumab in 2 (<0.1%) patients. Hyperthyroidism resolved in

71 (74%) patients.

Hypothyroidism occurred in 237 (8.5%) patients, including Grade 2 or 3 cases in 174 (6.2%) and 3 (0.1%) patients, receiving pembrolizumab. The median time to onset of hypothyroidism was 3.5 months (range 1 day to 18.9 months). The median duration was not reached (range 2 days to 27.7+ months). One patient (< 0.1%) discontinued pembrolizumab due to hypothyroidism. Hypothyroidism resolved in 48 (20%) patients.

Immunogenicity
In clinical studies in patients treated with pembrolizumab 2 mg/kg every 3 weeks or 10 mg/kg every two or three weeks, 19 (1.7%) of 1,087 evaluable patients tested positive for treatment-emergent antibodies to pembrolizumab. There was no evidence of an altered pharmacokinetic or safety profile with anti-pembrolizumab binding antibody development.

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
Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell 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. Pembrolizumab 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-001 Non-Small Cell Lung Carcinoma
The efficacy of pembrolizumab was investigated in a multicentre, open-label, randomised, dose-comparative cohort of KEYNOTE-001. The trial excluded patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks. Patients were randomised to receive 10 mg/kg of pembrolizumab every 2 or 3 weeks until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Assessment of tumour status was performed every 9 weeks. The major efficacy outcome measures were ORR (according to RECIST 1.1 as assessed by blinded independent central review) and duration of response.

Treatment-Naïve NSCLC subjects
NSCLC patients had PD-L1 positive expression, defined as a tumour proportion score (TPS) ≥ 50% as ascertained retrospectively by the PD-L1 IHC 22C3 pharmDx™ kit. This cohort excluded patients with EGFR or ALK genomic tumour aberrations. Among the treatment-naïve patients with tumour samples evaluable for PD-L1 expression, 17 had TPS ≥ 50%. The baseline characteristics for this population included: median age 70 years (56% age 65 or older); 50% male; 100% White; and 56% and 44% with an ECOG performance status 0 and 1, respectively. Disease characteristics were squamous and non-squamous (6% and 88%, respectively) and M1 (88%).

Efficacy results for this cohort are summarised in Table 3

Table 3: Response to pembrolizumab 10 mg/kg every 2 or 3 Weeks in treatment-naïve NSCLC Patients with PD-L1 TPS ≥50% (n=17)

Endpoint	
Best Overall Response*	
ORR %, (95% CI)	47% (23, 72)†
Response Duration‡	
Median in months (range)	Not reached (4.2+, 7.7+)
% ongoing	88%§
Time to Response‡	
Median in months (range)	2.1 (1.7, 2.9)
PFS¶	
Median in months (95% CI)	Not reached (2.4, NA)
6-month PFS rate	76%
OS¶	
6-month OS rate	94%

* Based on all patients treated (n=17), with assessment by independent review and RECIST 1.1
† All responses were partial responses
‡ Based on patients (n=8) with a confirmed response by independent review
§ Includes 4 patients with ongoing responses of 6 months or longer
¶ Based on all treated patients (n=17)
NA = not available

5.2 Pharmacokinetic properties

The pharmacokinetics of pembrolizumab was studied in 2856 patients with metastatic or unresectable melanoma, NSCLC, 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 (~7.4 L; CV: 19%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

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

Elimination
The systemic clearance of pembrolizumab is ~0.2 L/day (CV: 37%) and the terminal half-life ($t_{½}$) is ~27 days (CV: 38%).

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 2.2-fold when administered every 3 weeks. Near steady-state concentrations of pembrolizumab were achieved by 18 weeks; the median Cmin at 18 weeks was approximately 24 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, race, mild or moderate renal impairment, mild hepatic impairment, and tumour burden.

Renal Impairment
The effect of renal impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analysis 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 analysis 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.

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 fetus thoughout pregnancy. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss.

Animal 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
2 years

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 pembrolizumab. Each vial contains an excess fill of 10 mg (0.4mL) to ensure the recovery of 50 mg of pembrolizumab per vial. After reconstitution, 1 mL of concentrate contains 25 mg of pembrolizumab.
- 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 pembrolizumab 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 pembrolizumab 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.
- Pembrolizumab 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. SCIENTIFIC OPINION HOLDER

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

8. EAMS NUMBER

00025/0001

9 DATE OF SCIENTIFIC OPINION

March 2016

Additional information

- Each prescribing oncologist will be provided with a **physician pack** containing all the relevant documents needed to manage patients receiving pembrolizumab under EAMS.
- As each patient signs the Informed Consent Form, they must be issued with a **Patient Alert Card**. This is a wallet-card sized and patients must be instructed to carry it with them at all times. It summarises the important side effects which they need to seek assistance for. In addition it alerts any other healthcare professional that may treat them, that the patient is receiving pembrolizumab through an early access scheme, with details of their own oncologist, specialist nurse, out of hours contact details and the Company's contact details.
- Prescribers will be provided with guidance on managing Adverse Events including immune-related adverse events and dose management.
- A dose calculator is provided.

Contact information

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