

KEYTRUDA®▼ (pembrolizumab)

PRESCRIBING INFORMATION

Refer to Summary of Product Characteristics (SmPC) before prescribing

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to MSD, UK (Tel: 01992 467272) By clicking the above link you will leave the MSD website and be taken to the MHRA website.

PRESENTATION:

50 mg powder for concentrate for solution for infusion (1 vial contains 50 mg pembrolizumab)

25 mg/mL concentrate for solution for infusion (1 vial of 4 mL contains 100 mg of pembrolizumab)

USES: MONOTHERAPY:

Advanced (unresectable or metastatic) melanoma in adults.

Adjuvant treatment of Stage III melanoma in adults with lymph node involvement who have undergone complete resection.

First-line metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a $\geq 50\%$ tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.

Locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a $\geq 1\%$ TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before treatment. Adults with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. Locally advanced or metastatic urothelial carcinoma (UC) in adults who have received prior platinum-containing chemotherapy or who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 . Recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a $\geq 50\%$ TPS and progressing on or after platinum-containing chemotherapy.

COMBINATION THERAPY:

With pemetrexed and platinum chemotherapy, for first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.

DOSAGE AND ADMINISTRATION: See SmPC for full details. Therapy must be initiated and supervised by specialist

physicians experienced in the treatment of cancer.

NSCLC: Testing for PD-L1 expression using a validated test is recommended. In non-squamous NSCLC with high PD-L1 expression, consider the risk of adverse reactions with combination therapy relative to monotherapy. Evaluate benefit/risk of the combined therapy on an individual basis.

Untreated UC or HNSCC: Select for treatment based on PD-L1 expression confirmed by a validated test.

Recommended dose is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks.

Treat patients until disease progression or unacceptable toxicity. For adjuvant treatment of melanoma, administer until disease recurrence, unacceptable toxicity, or for up to one year.

Special populations: Renal impairment: No dose adjustment needed for mild or moderate renal impairment. No studies in severe renal impairment. *Hepatic impairment:* No dose adjustment needed for mild hepatic impairment. No studies in moderate or severe hepatic impairment. *Ocular melanoma:* Limited data. *Paediatric population:* Safety and efficacy in children below 18 years of age not established.

Eastern Cooperative Oncology Group (ECOG) performance status score ≥ 2 : Patients with ECOG ≥ 2 were excluded from clinical trials of melanoma, NSCLC, cHL and HNSCC. *Elderly:* Data in patients ≥ 75 years are limited. No dose adjustment necessary for monotherapy.

Administer pembrolizumab first when used in combination with pemetrexed and platinum chemotherapy. See SmPCs for pemetrexed and the selected platinum chemotherapy.

CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS: See SmPC for full details. To improve traceability of biologics, record the name and the batch number.

Immune-related adverse reactions: Severe and fatal cases have occurred. 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. Immune related adverse reactions affecting more than one body system can occur simultaneously. Immune-related pneumonitis: Monitor for pneumonitis. Confirm suspected pneumonitis radiographically. Exclude other causes. Administer corticosteroids for Grade ≥ 2 events. For Grade 2 events withhold pembrolizumab until recovery to Grade 0 or 1. For Grade 3, 4 or recurrent Grade 2 discontinue pembrolizumab. Pneumonitis occurred more frequently in patients with prior thoracic radiation. Immune-related colitis: Monitor for colitis and exclude other causes. Administer corticosteroids for Grade ≥ 2 events. Consider the potential risk of gastrointestinal perforation. For Grade 2 or 3 events withhold pembrolizumab until recovery to Grade 0 or 1. For Grade 4 events or recurrent Grade 3 events permanently discontinue pembrolizumab. Immune-related hepatitis: Monitor for changes in liver function (at baseline, periodically and based on clinical evaluation) and symptoms of hepatitis. Exclude other causes. Administer corticosteroids for Grade ≥ 2 events. For hepatitis with AST or ALT > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN (Grade 2), withhold pembrolizumab until recovery to Grade 0 or 1. For hepatitis with AST or ALT > 5 times ULN or total bilirubin > 3 times ULN (Grade ≥ 3), discontinue pembrolizumab permanently. With liver metastasis with baseline Grade 2 elevation of AST or ALT, or hepatitis with AST or ALT increases $\geq 50\%$ and lasting ≥ 1 week, discontinue pembrolizumab permanently. Immune-related nephritis: Monitor patients for changes in renal function. Exclude other causes of renal dysfunction. Administer corticosteroids for Grade ≥ 2 events. For Grade 2 nephritis with creatinine > 1.5 to ≤ 3 times ULN, withhold pembrolizumab until recovery to Grade 0 or 1. For Grade ≥ 3 nephritis with creatinine > 3 times ULN, discontinue pembrolizumab permanently. Immune-related endocrinopathies: For patients with Grade 3 or Grade 4 endocrinopathy that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, consider continuation of pembrolizumab after corticosteroid taper, if needed. Otherwise discontinue treatment. Long-term hormone replacement therapy may be necessary in cases of immune-related endocrinopathies.

Monitor for hypophysitis (including hypopituitarism and secondary adrenal insufficiency). Exclude other causes. Administer corticosteroids to treat secondary adrenal insufficiency and other hormone replacement as clinically indicated. Withhold pembrolizumab for symptomatic hypophysitis until the event is controlled with hormone replacement. Consider continuation of pembrolizumab, after corticosteroid taper, if needed. Monitor pituitary function and hormone levels. Monitor for hyperglycaemia or other signs and symptoms of diabetes. Withhold pembrolizumab in cases of Grade 3 hyperglycaemia until metabolic control is achieved. Monitor for changes in thyroid function. Manage hypothyroidism with replacement therapy without treatment interruption and without corticosteroids. Hypothyroidism is more frequently reported in patients with HNSCC with prior radiation therapy. Manage hyperthyroidism symptomatically. Withhold pembrolizumab for Grade ≥ 3 hyperthyroidism until recovery to Grade ≤ 1 . For Grade 3 or 4 hyperthyroidism that improved to Grade 2 or lower, consider continuation of pembrolizumab, after corticosteroid taper. Immune-related skin reactions: Monitor for suspected severe skin reactions and exclude other causes. Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported. For Grade 3 or suspected SJS or TEN, withhold pembrolizumab until recovery to Grade 0 or 1. For Grade 4 or confirmed SJS or TEN, discontinue pembrolizumab permanently. For signs or symptoms of SJS or TEN refer patient to a specialised unit for assessment and treatment. Use with caution when considering use in patients who have previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents. Other clinically significant immune-related adverse reactions: uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, haemolytic anaemia, sarcoidosis and encephalitis have been reported in clinical trials or in post-marketing experience. Based on the severity of the adverse reaction, withhold pembrolizumab and administer corticosteroids. Pembrolizumab may be restarted 12 weeks after last dose if the adverse reaction remains at Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day. Discontinue pembrolizumab for any Grade 3 event that recurs and for any Grade 4 event

except haematological toxicity in patients with cHL in which pembrolizumab should be withheld until adverse reactions recover to Grade 0-1. For Grade 3 or Grade 4 myocarditis, encephalitis or Guillain-Barré syndrome discontinue pembrolizumab permanently. Solid organ transplant rejection has been reported in patients treated with PD-1 inhibitors. Consider the benefit of treatment with pembrolizumab versus the risk of possible organ rejection in these patients.

Infusion-related reactions: For severe infusion reactions, including hypersensitivity and anaphylaxis (Grade 3 or 4), stop infusion permanently. With mild or moderate infusion reactions continue infusion with close monitoring.

If treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose of pembrolizumab, or if corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks, permanently discontinue therapy.

Complications of allogeneic Haematopoietic Stem Cell Transplant (HSCT): Allogeneic HSCT after treatment with pembrolizumab: Cases of graft-versus-host-disease (GVHD) and hepatic veno-occlusive disease (VOD) have been observed in patients with cHL undergoing allogeneic HSCT after previous exposure to pembrolizumab. The potential benefits of HSCT and the possible increased risk of transplant-related complications should be considered case by case. Allogeneic HSCT prior to treatment with pembrolizumab:

Acute GVHD, sometimes fatal has been reported after treatment with pembrolizumab. Patients who experienced GVHD after their transplant procedure may be at an increased risk for GVHD after treatment with pembrolizumab. Consider the benefit of treatment versus the risk of possible GVHD in patients with a history of allogeneic HSCT.

Disease-specific precautions:

Urothelial carcinoma patients who have received prior platinum-containing chemotherapy: Consider the delayed onset of pembrolizumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In urothelial cancer, a higher number of deaths within 2 months was observed in pembrolizumab compared to chemotherapy. Factors associated with early deaths were fast progressive disease on prior platinum therapy and liver metastases.

Urothelial cancer for patients who are considered ineligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with CPS ≥ 10 : No safety and efficacy

data are available in frailer patients (e.g., ECOG performance status 3) therefore use caution in this population and consider the potential risk-benefit on an individual basis.

Use of pembrolizumab in combination with chemotherapy for first-line treatment of patients with NSCLC

The frequency of adverse reactions for pembrolizumab combination therapy is observed to be higher than for pembrolizumab monotherapy or chemotherapy alone. Use with caution when treating patients ≥ 75 years, with combination therapy. Consider the potential benefit/risk on an individual basis.

Adjuvant treatment of melanoma in patients ≥ 75 years: A trend towards an increased frequency of severe and serious adverse reactions. Safety data are limited.

Drug interactions: No formal pharmacokinetic drug interaction studies have been conducted. No metabolic drug-drug interactions are expected. Avoid use of systemic corticosteroids or immunosuppressants before starting pembrolizumab because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab but may be used after starting pembrolizumab to treat immune related adverse reactions.

Pregnancy: No data on use in pregnant women. Do not use during pregnancy unless the clinical condition requires treatment with pembrolizumab. Women of childbearing potential should use effective contraception during treatment and for at least 4 months after the last dose of pembrolizumab.

Breast-feeding: It is unknown whether pembrolizumab is secreted in human milk. The decision whether to discontinue breast-feeding or the drug, should balance the benefit of breast-feeding against that of treatment for the woman.

SIDE EFFECTS: Refer to SmPC for complete information on side effects.

Pembrolizumab is most commonly associated with immune-related adverse reactions. Most serious adverse reactions were immune and infusion-related adverse reactions. **Monotherapy:** Very Common: anaemia, hypothyroidism, decreased appetite, headache, dyspnoea, cough, diarrhoea, abdominal pain, nausea, vomiting, constipation, rash, pruritus, musculoskeletal pain, arthralgia, fatigue, asthenia, oedema, pyrexia.

Common: pneumonia, thrombocytopenia, lymphopenia, infusion-related reaction, hyperthyroidism, hyponatraemia, hypokalaemia, hypocalcaemia, insomnia, dizziness,

neuropathy peripheral, lethargy, dysgeusia, dry eye, hypertension, pneumonitis, colitis dry mouth, severe skin reactions, erythema, alopecia, eczema, dermatitis acneiform, vitiligo, dry skin, myositis, pain in extremity, arthritis, influenza like illness, chills, ALT and AST increases, hypercalcaemia, increase in blood alkaline phosphatase, blood bilirubin and blood creatinine. **Serious:** *Uncommon:* neutropenia, leukopenia, eosinophilia, sarcoidosis, type 1 diabetes mellitus, epilepsy, pericardial effusion, pericarditis, pancreatitis. *Rare:* immune thrombocytopenic purpura, haemolytic anaemia, pure red cell aplasia, myasthenic syndrome, encephalitis, Vogt-Koyanagi-Harada syndrome, myocarditis, small intestinal perforation, meningitis (aseptic).

Combination with chemotherapy: *Very Common:* anaemia, neutropenia, thrombocytopenia, decreased appetite, dysgeusia, diarrhoea, nausea, vomiting, constipation, rash, pruritus, fatigue, asthenia, oedema, ALT increase. *Common:* pneumonia, febrile neutropenia, leukopenia, lymphopenia, infusion related reaction, hypothyroidism, hyperthyroidism, hypokalaemia, hyponatraemia, hypocalcaemia, dizziness, headache, lethargy, neuropathy peripheral, dry eye,

pneumonitis, dyspnoea, cough, colitis, abdominal pain, dry mouth, hepatitis, severe skin reactions, alopecia, dermatitis acneiform, dry skin, erythema, arthralgia, myositis, arthritis, musculoskeletal pain, pain in extremity, nephritis, acute kidney injury, pyrexia, increase in AST, blood alkaline phosphatase and blood creatinine. **Serious:** *Uncommon:* type 1 diabetes mellitus, pericardial effusion, hypertension, pancreatitis, amylase increased, hypercalcaemia.

PACKAGE QUANTITIES AND BASIC NHS COST:

50 mg powder for concentrate for solution for infusion 1 vial: £1315.00

25 mg/mL concentrate for solution for infusion 1 vial: £2630.00

Marketing Authorisation numbers:

50 mg powder for concentrate for solution for infusion - EU/1/15/1024/001

25 mg/mL concentrate for solution for infusion 1 vial - EU/1/15/1024/002

Marketing Authorisation Holder:

Merck Sharp & Dohme B.V. Waarderweg 39, 2031 BN Haarlem, The Netherlands.

Legal Category: POM

Date of review of prescribing information: January 2019

© Merck Sharp & Dohme Limited 2019. All rights reserved.

PI.KTD.19.UK.6688-PSUSA-00010403-201803 (Combined)