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 (Tel: 01992 467272), United Kingdom.
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: As monotherapy, for the treatment of advanced (unresectable or metastatic) melanoma in adults. Also for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. Also for treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥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. Also as monotherapy for the treatment of adult patients 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. Also as monotherapy for the treatment of 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. NSCLC and previously untreated UC patients should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test.

DOSAGE AND ADMINISTRATION: See SmPC for full details. Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer.
Administer as an intravenous infusion over 30 minutes every 3 weeks.
Recommended dose is:
200 mg for NSCLC that has not been previously treated with chemotherapy, for cHL or for urothelial carcinoma.
2 mg/kg for NSCLC that has been previously treated with chemotherapy or for melanoma.
Treat patients until disease progression or unacceptable toxicity. *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 and cHL. *Elderly:* No dose adjustment necessary (data in cHL patients ≥ 65 years is too limited to draw conclusions).

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

PRECAUTIONS: See SmPC for full details. *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. Immune related adverse reactions affecting more than one body system can occur simultaneously. *Immune-related pneumonitis:* Fatal cases have been reported. 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. *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 ≥ 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. 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), some with fatal outcome, 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 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 including severe and fatal cases 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) i: 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.

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. *Very Common:* diarrhoea, nausea, rash, pruritus, fatigue. *Common:* anaemia, infusion-related reaction, hyperthyroidism, hypothyroidism, decreased appetite, headache, dizziness, dysgeusia, pneumonitis, dyspnoea, cough, colitis, vomiting, abdominal pain, constipation, dry mouth, severe skin reactions, vitiligo, dry skin, erythema, arthralgia, myositis, musculoskeletal pain, pain in extremity, arthritis, asthenia, oedema, pyrexia, influenza like illness, chills, ALT and AST increases, increase in blood alkaline phosphatase, increase in blood creatinine**.** Serious: *Uncommon:* pneumonia, neutropenia, thrombocytopenia, leukopenia, lymphopenia, eosinophilia, type 1 diabetes mellitus, hyponatraemia, hypokalaemia, hypocalcaemia, epilepsy, neuropathy peripheral, hypertension, hypercalcaemia, eczema, myocarditis, pericarditis, pericardial effusion. *Rare:* immune thrombocytopenic purpura, haemolytic anaemia, sarcoidosis, encephalitis, small intestinal perforation.

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

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