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:
25 mg/mL concentrate for solution for infusion (1 vial of 4 mL contains 100 mg of pembrolizumab)
50 mg powder for concentrate for solution for infusion (1 vial contains 50 mg 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 ≥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 ≥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.
- First-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1
- Recurrent or metastatic HNSCC in adults whose tumours express PD-L1 with a ≥ 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.
- With carboplatin and either paclitaxel or nab-paclitaxel for first-line treatment of metastatic squamous NSCLC in adults.
- With axitinib for first-line treatment of advanced renal cell carcinoma (RCC) in adults.
- With platinum and 5-fluorouracil (5-FU) chemotherapy for the first-line treatment of metastatic or unresectable recurrent HNSCC in adults whose tumours express PD-L1 with a CPS ≥ 1

DOSAGE AND ADMINISTRATION: See SmPC for full details. Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer.
Testing for PD-L1 expression using a validated test is recommended to select patients for monotherapy treatment for NSCLC, HNSCC or untreated UC, and for combination therapy for HNSCC.
For combination treatment with axitinib in RCC, consider dose escalation of axitinib above the initial 5 mg dose at 6 weekly intervals or longer. See SmPC for axitinib to determine the dosage.
Administer as an IV infusion over 30 minutes.
Recommended dose: monotherapy: 200 mg every 3 weeks or 400mg every 6 weeks.
combination therapy: 200 mg every 3 weeks.
Treat 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. *Paediatric population:* Safety and efficacy in children below 18 years of age not established.

Elderly: No dose adjustment necessary. Data from chemotherapy combination in NSCLC, axitinib combination in RCC, monotherapy in resected Stage III melanoma and first-line monotherapy or chemotherapy combination in metastatic or unresectable recurrent HNSCC patients ≥ 75 years are limited. Data from cHL patients ≥ 65 years are limited.
Administer pembrolizumab first when used in combination with intravenous chemotherapy. When used in combination see SmPCs for concomitant therapies to determine the dosage.
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.
Evaluate suspected immune-related adverse reactions to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, initiate corticosteroid taper and continue 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. Restart treatment with pembrolizumab within 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. Permanently discontinue pembrolizumab 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.
Immune-related pneumonitis, colitis, hepatitis, nephritis, endocrinopathies and skin conditions have been observed with pembrolizumab treatment. Other clinically significant immune-related adverse reactions include uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, haemolytic anaemia, sarcoidosis, encephalitis and myelitis. Solid organ transplant rejection has been reported. Consider the benefit of treatment with pembrolizumab versus the risk of possible organ rejection in these patients. Refer to SmPC for full details of potential immune-related adverse reactions and their management.
Infusion-related reactions: Severe infusion-related reactions, including hypersensitivity and anaphylaxis, have been reported in patients receiving pembrolizumab. For severe infusion reactions, stop the infusion and permanently discontinue pembrolizumab. For mild or moderate infusion reactions, patients may continue to receive treatment with close monitoring. Consider premedication with antipyretic and antihistamine.
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.) Use caution in this population and consider the potential risk-benefit on an individual basis.

First-line treatment of patients with NSCLC: The frequency of adverse reactions for combination therapy is observed to be higher than for pembrolizumab monotherapy or chemotherapy alone. Consider the benefit/risk balance of monotherapy or combination therapy before initiating treatment in previously untreated patients with NSCLC whose tumours express PD-L1. Use 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.

With axitinib for first-line treatment of patients with RCC: Combination treatment results in higher than expected frequencies of Grades 3 and 4 ALT and AST elevations. Monitor liver enzymes before and periodically throughout treatment. Consider more frequent monitoring than with monotherapy.

First-line treatment of patients with HNSCC: Frequency of adverse reactions in combination therapy is higher than for monotherapy or chemotherapy alone. Consider the benefit/risk of treatment options before initiating treatment.

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. Corticosteroids can also be used as premedication, when pembrolizumab is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-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, thrombocytopaenia, lymphopaenia, infusion-related reaction, hyperthyroidism, hyponatraemia, hypokalaemia, hypocalcaemia, insomnia, dizziness, neuropathy peripheral, lethargy, dysgeusia, dry eye, cardiac arrhythmia (including atrial fibrillation), 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:* neutropaenia, leukopaenia, eosinophilia, sarcoidosis, hypophysitis, adrenal insufficiency, type 1 diabetes mellitus, epilepsy, pericardial effusion, pericarditis, pancreatitis, gastrointestinal ulceration, hepatitis nephritis. *Rare:* Guillain-Barré syndrome, myelitis, toxic epidermal necrolysis, immune thrombocytopenic purpura, haemolytic anaemia, pure red cell aplasia, haemophagocytic lymphohistiocytosis, myasthenic syndrome, encephalitis, Vogt-Koyanagi-Harada syndrome, myocarditis, small intestinal perforation, Stevens-Johnson syndrome, meningitis (aseptic).

Combination with chemotherapy: *Very Common:* anaemia, neutropaenia, thrombocytopaenia, hypokalaemia, decreased appetite, dizziness, neuropathy peripheral, dysgeusia, headache, dyspnoea, cough, diarrhoea, nausea, vomiting, constipation, abdominal pain, rash, alopecia, pruritus, musculoskeletal pain, arthralgia, fatigue, asthenia, oedema, pyrexia and blood creatinine increase. *Common:* pneumonia, febrile neutropaenia, leukopaenia, lymphopaenia, infusion related reaction, hypothyroidism, hyperthyroidism, hypocalcaemia, insomnia, hyponatraemia, lethargy, dry eye, hypertension, pneumonitis, colitis, dry mouth, severe skin reactions, dry skin, cardiac arrhythmia (including atrial fibrillation) erythema, myositis, pain in

extremity, arthritis, nephritis, acute kidney injury, chills, influenza-like illness, increase in ALT, AST and blood alkaline phosphatase hypercalcaemia. **Serious**: *Uncommon:* hypophysitis, adrenal insufficiency, type 1 diabetes mellitus, epilepsy, pericardial effusion, hepatitis, pancreatitis, gastrointestinal ulceration, hepatitis, amylase and blood bilirubin increased. **Rare:** eosinophilia, myocarditis, pericarditis.
Combination with axitinib: *Very common:* hyperthyroidism, hypothyroidism, decreased appetite, headache, dysgeusia**,** hypertension, dyspnoea, cough, dysphonia, diarrhoea, abdominal pain, nausea, vomiting, constipation, palmar-plantar erythrodysaesthesia syndrome, rash, pruritus, musculoskeletal pain, arthralgia, pain in extremity, fatigue, asthenia, pyrexia, ALT and AST increased, blood creatinine increased. *Common:* pneumonia, anaemia, neutropaenia, leukopaenia, thrombocytopaenia, infusion related reaction, hypophysitis, thyroiditis, adrenal insufficiency, hypokalaemia, hyponatraemia, hypocalcaemia, insomnia, dizziness, lethargy, neuropathy peripheral, dry eye, cardiac arrhythmia (including atrial fibrillation), pneumonitis, colitis, dry mouth, hepatitis, severe skin reactions, dermatitis acneiform, dermatitis, dry skin, alopecia, eczema, erythema, myositis, arthritis, tenosynovitis, acute kidney injury, nephritis, oedema, influenza like illness, chills, blood ALP increased, hypercalcaemia, blood bilirubin increased. **Serious:** *Uncommon:* lymphopaenia, eosinophilia, type 1 diabetes mellitus, myasthenic syndrome, myocarditis, pancreatitis, gastrointestinal ulceration, amylase increased.

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 1 vial - 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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