KEYTRUDA®
(pembrolizumab)

Healthcare Professional

Frequently Asked Questions

▼ 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.

MSD

Before prescribing KEYTRUDA, please read the accompanying Summary of Product Characteristics.

Contents

How should I **use this brochure?**

Please review the Summary of Product Characteristics for KEYTRUDA® (pembrolizumab) as well as this educational brochure prior to prescribing KEYTRUDA. Together, they will enable you to understand how KEYTRUDA is used, and will help you to:

- Understand potential adverse reactions
- Appropriately manage adverse reactions
- Utilize the Patient Information Brochure and Patient Alert Card with patients
- Ensure that adverse reactions are adequately and appropriately reported

This educational material is mandatory as a condition of the marketing authorization. The information in this brochure is provided by Merck Sharp & Dohme (MSD) for oncologists, oncology nurses, oncology pharmacists, and other healthcare professionals (HCPs) who are involved in the treatment of patients who are receiving KEYTRUDA. Healthcare professionals are asked to report any suspect adverse reactions. See page 13 of this brochure for how to report adverse reactions.

What is **KEYTRUDA® (pembrolizumab)?**

KEYTRUDA is a humanized monoclonal antibody that 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 antitumor 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 tumors or other cells in the tumor microenvironment.

What is KEYTRUDA indicated for?

For the approved indications of KEYTRUDA, please refer to the accompanying Summary of Product Characteristics.

KEYTRUDA is contraindicated in any patients with hypersensitivity to the active substance, pembrolizumab, or to any of following excipients: L-histidine, L-histidine hydrochloride monohydrate, sucrose, or polysorbate 80.

How is **KEYTRUDA® (pembrolizumab) administered?**

- Treatment must be initiated and supervised by a specialist physician experienced in the treatment of cancer.
- For the recommended dose of KEYTRUDA, please refer to the accompanying Summary of Product Characteristics. Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity.
- Atypical responses (ie, an initial transient increase in tumor size or small new lesions within the first few months, followed by tumor 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.

Pregnancy and lactation

Advise women of childbearing potential that they should use effective contraception during treatment with KEYTRUDA and for at least 4 months after the last dose. KEYTRUDA should not be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab.

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

Adverse **reactions**

What adverse reactions may be associated with treatment with KEYTRUDA® (pembrolizumab)?

The safety of KEYTRUDA has been evaluated in 3,830 patients with advanced melanoma, non-small cell lung carcinoma (NSCLC), classical Hodgkin lymphoma (cHL) or urothelial carcinoma across 4 doses (2 mg/kg every 3 weeks, 200 mg 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 KEYTRUDA were fatigue (21%), pruritus (16%), rash (13%), diarrhoea (12%) and nausea (10%). The majority of adverse reactions reported were of Grade 1 or 2 severity. The most clinically relevant adverse reactions were immune-related adverse reactions and severe infusion-related reactions.

Immune-related adverse reactions

Most immune-related adverse reactions occurring during treatment with KEYTRUDA were reversible and managed with interruptions of KEYTRUDA, administration of corticosteroids, and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of KEYTRUDA. Immune-related adverse reactions affecting more than one body system can occur simultaneously.

The following immune-related adverse reactions, including severe and fatal cases, have been reported in patients treated with KEYTRUDA in clinical trials or in post-marketing experience:

- Immune-related pneumonitis
- Immune-related colitis
- Immune-related hepatitis
- Immune-related nephritis
- Immune-related endocrinopathies (including hypophysitis, type 1 diabetes mellitus including diabetic ketoacidosis, hypothyroidism, hyperthyroidism, and thyroiditis)
- Immune-related skin adverse reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
- Other immune-related adverse reactions (uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, solid organ transplant rejection following pembrolizumab treatment in donor organ recipients, myasthenic syndrome, hemolytic anemia, sarcoidosis and encephalitis

Infusion-related reactions

Severe infusion-related reactions have been reported in patients receiving KEYTRUDA.

Complications of allogeneic haematopoietic stem cell transplant (HSCT)

Complications of allogeneic HSCT including graft-versus-host-disease (GVHD) have been observed in patients who have previously received pembrolizumab for haematologic malignancies or after pembrolizumab administration in patients with a history of allogeneic HSCT,

The frequencies of immune-related adverse reactions and infusion-related reactions are reported in section 4.8 of the Summary of Product Characteristics for KEYTRUDA.

Adverse **reactions**

How should I monitor for and manage immune-related adverse reactions in patients receiving KEYTRUDA® (pembrolizumab)?

Discuss immune-related and other adverse reactions that can occur during treatment with KEYTRUDA with your patient prior to initiating treatment.

For suspected immune-related adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reactions:

- Withhold KEYTRUDA and administer corticosteroids. Upon improvement to Grade ≤1, initiate corticosteroid taper and continue to taper over at least 1 month.
- Consider to restart KEYTRUDA within 12 weeks after last dose of KEYTRUDA if the adverse reaction remains at Grade ≤1 and corticosteroid dose is ≤10 mg prednisone or equivalent per day..
- Permanently discontinue KEYTRUDA if any Grade ≥3 toxicity occurs a second time and for any Grade 4 immune-related adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones or haematological toxicity, only in patients with cHL, in whom KEYTRUDA should be withheld until adverse reactions recover to Grade 0-1.
- Permanently discontinue KEYTRUDA for Grade 3 or 4 myocarditis, encephalitis or Guillain-Barré syndrome.
- 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.

	Monitor
Immune-related pneumonitis	• For signs and symptoms of pneumonitis. • Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded.
Immune-related colitis	• For signs and symptoms of colitis; exclude other causes.
Immune-related hepatitis	• For changes in liver function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and symptoms of hepatitis; exclude other causes.
Immune-related nephritis	• For changes in renal function; exclude other causes.
Immune-related endocrinopathies	• For signs and symptoms of hypophysitis including hypopituitarism and secondary adrenal insufficiency); exclude other causes. • For hyperglycemia or other signs and symptoms of diabetes. • 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.
Immune-related skin adverse reactions	• For signs and symptoms of severe skin reactions (including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)), exclude other causes.

Infusion-related reactions

Severe infusion-related reactions have been reported in patients receiving KEYTRUDA, including drug hypersensitivity, anaphylactic reaction, hypersensitivity, and cytokine release syndrome.

How should infusion-related reactions be treated?

- For severe infusion reactions, stop infusion and permanently discontinue KEYTRUDA.
- Patients with a mild or moderate infusion reaction may continue to receive KEYTRUDA with close monitoring.
- Premedication with antipyretic and antihistamine may be considered.

	Manage
Immune-related pneumonitis	• Administer corticosteroids for Grade ≥2 events (initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper). • Withhold KEYTRUDA for Grade 2 pneumonitis. • Permanently discontinue KEYTRUDA for Grade 3, Grade 4, or recurrent Grade 2 pneumonitis.
Immune-related colitis	• Administer corticosteroids for Grade ≥2 events (initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper). • Withhold KEYTRUDA for Grade 2 or Grade 3 colitis. • Permanently discontinue KEYTRUDA for Grade 4 colitis.
Immune-related hepatitis	• Administer corticosteroids: - Grade 2: initial dose of 0.5–1 mg/kg/day prednisone or equivalent followed by a taper. - Grade ≥3: 1–2 mg/kg/day prednisone or equivalent followed by a taper. • Based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA.
Immune-related nephritis	• Administer corticosteroids for Grade ≥2 events (initial dose of 1–2 mg/kg/day prednisone or equivalent followed by a taper). • Based on severity of creatinine elevations: - Withhold KEYTRUDA for Grade 2. - Permanently discontinue KEYTRUDA for Grade 3 or Grade 4 nephritis.
Immune-related endocrinopathies	• Long-term hormone replacement therapy may be necessary in cases of immune-related endocrinopathies. • Administer corticosteroids to treat secondary adrenal insufficiency and other hormone replacement as clinically indicated. • Withhold KEYTRUDA for symptomatic hypophysitis until the event is controlled with hormone replacement. Pituitary function and hormone levels should be monitored to ensure appropriate hormone replacement. • Administer insulin for type 1 diabetes, and withhold KEYTRUDA in cases of Grade 3 hyperglycemia until metabolic control is achieved. • Hypothyroidism may be managed with replacement therapy without treatment interruption or corticosteroids. • Hyperthyroidism may be managed symptomatically. Withhold or discontinue KEYTRUDA for Grade 3 or Grade 4 hyperthyroidism. • For patients with Grade 3 or Grade 4 hyperthyroidism that improved to Grade 2 or lower, continuation of KEYTRUDA may be considered, after corticosteroid taper, if needed. Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement
Immune-related skin adverse reactions	• Withhold KEYTRUDA for Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). • Permanently discontinue KEYTRUDA for Grade 4 or confirmed SJS or TEN.

What is the **Patient Information Brochure?**

Important information about treatment with KEYTRUDA® (pembrolizumab) has been highlighted in a Patient Information Brochure. You may use the brochure as a guide to help initiate a discussion with the patient about treatment. Patients can review on their own as needed to better understand their treatment regimen.

In addition to providing an overview of treatment, the Patient Information Brochure outlines precisely what the patient should do when experiencing an adverse reaction (ie, immune-related adverse reaction or infusion-related reaction).

Included in each brochure is a Patient Alert Card, which patients must carry with them at all times and show at all medical visits to healthcare professionals other than the KEYTRUDA prescriber. Please direct the patient to complete all relevant sections of the card, including all contact information for the prescriber, patient, and any caregiver who plays a role in helping the patient. This card can be especially helpful in visits to emergency healthcare facilities, where the patient may be unknown.

Please take a moment to ensure patients understand how to use the Alert Card. See that it contains summary information about treatment and how to appropriately manage adverse reactions. Emphasize to patients the importance of completing the card and carrying it at all times.

Most important, patients should be reminded that if they do experience an adverse reaction, they should seek medical attention immediately and undergo prompt treatment.

Where can I **obtain additional information?**

More information about KEYTRUDA® (pembrolizumab) is available in the Summary of Product Characteristics, on the website of the European Medicines Agency (http://www.ema.europa.eu), or by calling Merck Sharp & Dohme, a subsidiary of Merck & Co, Inc., at **800 7 4433**.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 for KEYTRUDA at ADR Reporting at: www.medicinesauthority.gov.mt/adrportal.

Adverse events should also be reported to Merck Sharp & Dohme Cyprus Ltd by calling **800 7 4433** or at **malta_info@merck.com**.

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(pembrolizumab)

If you require any additional information regarding the use of KEYTRUDA, or would like to obtain additional copies of the educational materials, contact the Merck Sharp & Dohme Medical Information department at **800 7 4433** or at **malta_info@merck.com**.

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