

**PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS REGULATIONS
(PREPARATIONS) 1986**

This medicine is marketed upon physician's prescription only

KEYTRUDA[®] 100 mg/4 mL

Concentrate for Solution for intravenous Infusion

Each vial contains:
Pembrolizumab 100 mg

For a list of inactive ingredients see section 6.1 "What **KEYTRUDA** contains".

Read the entire leaflet carefully before you start using this medicine.

- This leaflet contains concise information about **KEYTRUDA**. If you have any further questions, refer to your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their medical condition seems similar to yours.

In addition to the leaflet, **KEYTRUDA** has a 'Patient Alert Card' and a 'Patient information Guide'. The card and guide include important safety information, that you need to know before starting and during the treatment with **KEYTRUDA** and act accordingly. Read the Patient Alert Card, Patient Information Guide and the patient leaflet before you start using this medicine. Keep the Patient Alert Card and Patient Information Guide for further reference if needed.

1. WHAT KEYTRUDA IS INTENDED FOR?

KEYTRUDA is a prescription medicine used to treat:

- skin cancer called melanoma. **KEYTRUDA** may be used:
 - when your melanoma has spread or cannot be removed by surgery (advanced melanoma), **or**
 - to help prevent melanoma from coming back after it and lymph nodes that contain cancer have been removed by surgery.
- lung cancer called non-small cell lung cancer (NSCLC).
 - **KEYTRUDA** may be used with the chemotherapy medicines pemetrexed and carboplatin as your first treatment when your lung cancer:
 - has spread (advanced NSCLC), **and**
 - is a type of lung cancer called "nonsquamous", **and**
 - your tumor does not have an abnormal "EGFR" or "ALK" gene.
 - **KEYTRUDA** may be used with the chemotherapy medicines carboplatin and either paclitaxel or paclitaxel protein-bound as your first treatment when your lung cancer:
 - has spread (advanced NSCLC), **and**
 - is a type called "squamous".
 - **KEYTRUDA** may be used alone when your lung cancer:
 - has spread (advanced NSCLC) **and**,
 - tests positive for "PD-L1" **and**,
 - as your first treatment if you have not received chemotherapy to treat your advanced NSCLC and your tumor does not have an abnormal "EGFR" or "ALK" gene,**or**
 - you have received chemotherapy that contains platinum to treat your advanced NSCLC, and it did not work or it is no longer working, **and**
 - if your tumor has an abnormal "EGFR" or "ALK" gene, you have also received an EGFR or ALK inhibitor medicine and it did not work or is no longer working.

- lung cancer called small cell lung cancer (SCLC). **KEYTRUDA** may be used when your lung cancer:
 - has spread (advanced SCLC), **and**
 - you have received 2 or more previous treatments, including chemotherapy that contains platinum, and they did not work or no longer working, and you have not been previously treated with immunotherapy.
- head and neck squamous cell cancer (HNSCC):
 - **KEYTRUDA** may be used with the chemotherapy medicines fluorouracil and a platinum as your first treatment when your head and neck cancer has spread or returned and cannot be removed by surgery.
 - **KEYTRUDA** may be used alone as your first treatment when your head and neck cancer:
 - has spread or returned and cannot be removed by surgery, **and**
 - your tumor tests positive for “PD-L1”.
 - **KEYTRUDA** may be used alone when your head and neck cancer:
 - has spread or returned, **and**
 - you have received chemotherapy that contains platinum, and it did not work or is no longer working.
- classical Hodgkin lymphoma (cHL):
 - in adults when:
 - your cHL has returned **or**
 - you have tried a treatment and it did not work, **or**
 - in children when:
 - you have tried a treatment and it did not work **or**
 - your cHL has returned after you received 2 or more types of treatment.
- primary mediastinal B-cell lymphoma (PMBCL) in adults and children when:
 - you have tried a treatment and it did not work **or**
 - your PMBCL has returned after you received 2 or more types of treatment.
- bladder and urinary tract cancer called urothelial carcinoma.
 - **KEYTRUDA** may be used when your cancer has not spread to nearby tissue in the bladder, but is at high-risk for spreading (high-risk non-muscle-invasive bladder cancer [NMIBC]) when:
 - your tumor is a type called “carcinoma in situ” (CIS), **and**
 - you have tried treatment with Bacillus Calmette-Guerin (BCG) and it did not work, **and**
 - you are not able to or have decided not to have surgery to remove your bladder.
 - **KEYTRUDA** may be used when your bladder or urinary tract cancer:
 - has spread or cannot be removed by surgery (advanced urothelial cancer) **and**
 - you are not able to receive chemotherapy that contains a medicine called cisplatin, and your tumor tests positive for “PD-L1”, **or**
 - you are not able to receive a medicine called cisplatin or carboplatin (regardless of PD-L1 status), **or**
 - the disease has progressed during or after you have received chemotherapy that contains platinum.
- cancer that is shown by a laboratory test to be a microsatellite instability-high (MSI-H) or a mismatch repair deficient (dMMR) solid tumor. **KEYTRUDA** may be used in adults and children to treat:
 - cancer that has spread or cannot be removed by surgery (advanced cancer), **and**
 - has progressed following systemic treatment, and you have no satisfactory treatment options, **or**
 - you have colon or rectal cancer, that has progressed although you have received chemotherapy treatment with fluoropyrimidine, oxaliplatin, and irinotecan.

It is not known if **KEYTRUDA** is safe and effective in children with MSI-H cancers of the brain or spinal cord (central nervous system cancers).

- colon or rectal cancer. **KEYTRUDA** may be used as your first treatment when your cancer:
 - has spread or cannot be removed by surgery (advanced colon or rectal cancer), **and**
 - has been shown by a laboratory test to be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

- stomach cancer called gastric or gastroesophageal junction (GEJ) adenocarcinoma that tests positive for “PD-L1”, when:
 - the cancer has returned or spread (advanced gastric cancer), **and**
 - you have received 2 or more types of chemotherapy including fluoropyrimidine and chemotherapy that contains platinum, **and**
 - if your tumor has an abnormal “HER2/neu” gene, and you also received a HER2/neu-targeted medicine.
- cancer called esophageal or certain gastroesophageal junction (GEJ) carcinomas. **KEYTRUDA** may be used with platinum- and fluoropyrimidine- based chemotherapy medicines when:
 - your cancer cannot be cured by surgery or a combination of chemotherapy and radiation therapy.
- cancer called squamous cell carcinoma of the esophagus. **KEYTRUDA** may be used when:
 - your cancer has returned or spread (advanced esophageal cancer), **and**
 - your tumor tests positive for “PD-L1” and you have received one or more types of treatment and it did not work or is no longer working.
- cervical cancer that tests positive for “PD-L1”. **KEYTRUDA** may be used when your cervical cancer:
 - has returned, or has spread or cannot be removed by surgery (advanced cervical cancer), **and**
 - you have received chemotherapy, and it did not work or is no longer working.
- a kind of skin cancer called Merkel cell carcinoma (MCC) in adults and children. **KEYTRUDA** may be used to treat your skin cancer when it has spread or returned.
- kidney cancer called renal cell carcinoma (RCC).
 - **KEYTRUDA** may be used with the medicine axitinib as your first treatment when your kidney cancer has spread or cannot be removed by surgery (advanced RCC).
 - **KEYTRUDA** may be used with the medicine lenvatinib as your first treatment when your kidney cancer has spread or cannot be removed by surgery (advanced RCC).
- a kind of uterine cancer called endometrial carcinoma.
 - **KEYTRUDA** may be used with the medicine lenvatinib:
 - when you have received anti-cancer treatment and it is no longer working, **and**
 - your cancer cannot be cured by surgery or radiation (advanced endometrial carcinoma).
- a kind of cancer that is shown by a test to be tumor mutational burden-high (TMB-H). **KEYTRUDA** may be used in adults and children to treat:
 - solid tumors that have spread or cannot be removed by surgery (advanced cancer), **and**
 - you have received anti-cancer treatment, and it did not work or is no longer working, **and**
 - you have no satisfactory treatment options.

It is not known if **KEYTRUDA** is safe and effective in children with TMB-H cancers of the brain or spinal cord (central nervous system cancers).
- skin cancer called cutaneous squamous cell carcinoma (cSCC). **KEYTRUDA** may be used when your skin cancer:
 - has returned or spread, **and**
 - cannot be cured by surgery or radiation.
- cancer called triple-negative breast cancer (TNBC). **KEYTRUDA** may be used with chemotherapy medicines when your breast cancer:
 - has returned and cannot be removed by surgery or has spread, **and**
 - tests positive for “PD-L1”.

Therapeutic group: Antineoplastic agents, humanized monoclonal antibody.

2. BEFORE USING KEYTRUDA

You should not be given KEYTRUDA:

if you are allergic to the active ingredient (pembrolizumab) or any of the other ingredients of this medicine (for a list of inactive ingredients, see section 6).

2.1 Special warnings regarding use of KEYTRUDA

Before starting treatment with KEYTRUDA, tell your doctor if you:

- have immune system problems such as Crohn’s disease, ulcerative colitis, or lupus
- have received an organ transplant, such as a kidney or liver
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have lung or breathing problems
- have liver problems
- have received radiation treatment to your chest area
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- have any other medical problems
- you are pregnant or plan to become pregnant (please refer to section 2.5 “pregnancy, breast-feeding and fertility”)

2.2 Children and Adolescents

KEYTRUDA is intended for children and adolescents under 18 years for classical Hodgkin lymphoma (cHL), primary mediastinal B-cell lymphoma (PMBCL), TMB-H cancer, MSI-H cancer or Merkel Cell Cancer (MCC), as safety and efficacy have been established in pediatric patients for use in these indications.

2.3 Tests and follow-up

During treatment with **KEYTRUDA** your doctor will do blood tests to check you for side effects.

2.4 Interactions with other medicines

If you are taking, or have recently taken, other medicines including non-prescription medicines and nutritional supplements, you should tell the doctor or pharmacist.

2.5 Pregnancy, breast-feeding and fertility

• **Pregnancy**

Before you receive **KEYTRUDA**, tell your doctor if you are pregnant or plan to become pregnant.

- **KEYTRUDA** can harm your unborn baby.

Females who are able to become pregnant:

- Your doctor will give you a pregnancy test before you start treatment with **KEYTRUDA**.
- You should use an effective method of birth control during and for at least 4 months after the final dose of **KEYTRUDA**. Talk to your doctor about birth control methods that you can use during this time.
- Tell your doctor right away if you think you may be pregnant or if you become pregnant during treatment with **KEYTRUDA**.

• **Breastfeeding**

Before you receive **KEYTRUDA**, tell your doctor if you are breastfeeding or plan to breastfeed.

- It is not known if **KEYTRUDA** passes into your breast milk.
- Do not breastfeed during treatment with **KEYTRUDA** and for 4 months after your final dose of **KEYTRUDA**.

3. HOW SHOULD YOU USE KEYTRUDA?

Always use **KEYTRUDA** as instructed by the doctor. You should check with your doctor or pharmacist if you are not sure regarding the dosage and treatment regimen.

The dosage and duration of treatment will be determined by the doctor only.

- Your doctor will give you **KEYTRUDA** into your vein through an intravenous (IV) line over 30 minutes.
- **KEYTRUDA** is usually given every 3 weeks.
- Your doctor will decide how many treatments you need.

Do not exceed the recommended dose.

If you have forgotten to take KEYTRUDA

If you miss any appointments, call your doctor as soon as possible to reschedule your appointment.

If you have further questions on the use of the medicine, consult with a doctor or a pharmacist.

4. SIDE EFFECTS

As with any medicine, **KEYTRUDA** may cause side effects, in some users.

Do not be alarmed by reading the list of side effects, you may not suffer from any of them.

KEYTRUDA is a medicine that may treat certain cancers by working with your immune system.

KEYTRUDA can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. You can have more than one of these problems at the same time. These problems may happen anytime during treatment or even after your treatment has ended.

Call or see your doctor right away if you develop any symptoms of the following problems or these symptoms get worse:

- **Lung problems (pneumonitis).** Symptoms of pneumonitis may include: shortness of breath; chest pain; cough.
- **Intestinal problems (colitis) that can lead to tears or holes in your intestine.** Signs and symptoms of colitis may include: diarrhea (loose stools) or more frequent bowel movements than usual; stools that are black, tarry, sticky, or have blood or mucus; severe stomach-area (abdomen) pain or tenderness.
- **Liver problems (hepatitis).** Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes; severe nausea or vomiting; pain on the right side of your stomach area (abdomen); dark urine (tea colored); feeling less hungry than usual; bleeding or bruising more easily than normal.
- **Hormone gland problems (especially the thyroid, pituitary, adrenal glands, and pancreas).** Signs and symptoms that your hormone glands are not working properly may include: rapid heartbeat; weight gain or weight loss; increased sweating; extreme tiredness; feeling more hungry or thirsty than usual; urinating more often than usual; hair loss; feeling cold; constipation; your voice gets deeper; muscle aches; feeling very weak; dizziness or fainting; headaches that will not go away or unusual headache; eye sensitivity to light; eye problems; changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness.
- **Kidney problems, including nephritis and kidney failure.** Signs of kidney problems may include: change in the amount or color of your urine; swelling of your ankles; loss of appetite.
- **Skin problems.** Signs of skin problems may include: rash; itching; blisters, peeling or skin sores; painful sores or ulcers in your mouth or in your nose, throat, or genital area; fever or flu-like symptoms; swollen lymph nodes.
- **Problems can also happen in other organs and tissues. These are not all of the signs and symptoms of immune system problems that can happen with KEYTRUDA. Call or see your doctor right away for any new or worsening signs or symptoms, which may include:**
 - shortness of breath, irregular heartbeat, feeling tired, swelling of ankles, or chest pain (myocarditis)
 - confusion, sleepiness, fever, muscle weakness, balance problems, nausea, vomiting, stiff neck, changes in mood or behavior, memory problems, or seizures (encephalitis), pain, muscle cramps, numbness, tingling, or numbness of the arms or legs, bladder or bowel problems, including the need to urinate more often, leaking of urine, trouble urinating, or constipation (myelitis),
 - changes in eyesight, vision changes, eye pain (sarcoidosis)
 - severe or persistent muscle or joint pains, severe muscle weakness
 - low red blood cells (anemia), bruising
 - swollen lymph nodes, rash or tender lumps on skin, cough
- **Infusion (IV) reactions that can sometimes be severe and life-threatening.** Signs and symptoms of infusion reactions may include: chills or shaking; shortness of breath or wheezing; itching or rash; flushing; dizziness; fever; feeling like passing out, back pain.

Rejection of a transplanted organ. People who have had an organ transplant may have an increased risk of organ transplant rejection. Your doctor should tell you what signs and symptoms you should report and monitor you, depending on the type of organ transplant that you have had.

Complications, including graft-versus-host-disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic). These complications can be severe and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with **KEYTRUDA**. Your doctor will monitor you for the following signs and symptoms: skin rash, liver inflammation, stomach-area (abdominal) pain, and diarrhea.

Getting medical treatment right away may help keep these problems from becoming more serious. Your doctor will check you for these problems during treatment with **KEYTRUDA**. Your doctor may treat you with corticosteroid or hormone replacement medicines. Your doctor may also need to delay or completely stop treatment with **KEYTRUDA**, if you have severe side effects.

Very common side effects of KEYTRUDA when used alone include:

(reported in greater than 10% of patients)

General: feeling tired, fever, weakness, weight loss, pain, flu-like illness

Skin and Subcutaneous Tissue: rash, skin discoloration, itching, swelling of arms or legs, swelling of face

Gastrointestinal: constipation, diarrhea, nausea, stomach area (abdominal) pain, increased liver enzymes in the blood, vomiting, swallowing difficulties

Musculoskeletal and Connective Tissue: joint pain, back pain, pain in muscles, bone or joints

Respiratory, Thoracic and Mediastinal: cough, shortness of breath

Metabolism and Nutrition: decreased appetite, decreased blood sodium

Endocrine: hypothyroidism (underactive thyroid)

Infections: upper respiratory tract infection, urinary tract infection (UTI), infection (except UTI)

Nervous System: headache, dizziness, inflammation of the nerves that may cause pain, weakness, and paralysis in the arms and legs

Cardiac: irregular heartbeat

Renal and Urinary: increased blood creatinine, blood in urine

Blood and Lymphatic System: decreased number of red blood cells

Vascular: bleeding

Common side effects of KEYTRUDA when used alone include:

(reported in 1% to 10 % of patients)

infusion reactions, overactive thyroid, inflammation of the lung, inflammation of the eye, inflammation of the muscles, inflammation of the covering of the heart, inflammation of the thyroid, accumulation of fluid around the heart, inflammation of the joints, mouth sores, pain in the neck, trouble sleeping and sudden kidney injury.

Uncommon side effects of KEYTRUDA when used alone include:

(reported in less than 1% of patients)

inflammation of the spinal cord and inflammation of the heart muscle.

Side effects of KEYTRUDA when used alone that are more common in children than in adults

include: fever, vomiting, upper respiratory tract infection, headache, and low levels of white blood cells and red blood cells (anemia).

Very common side effects of KEYTRUDA when given with certain chemotherapy medicines include:

(reported in greater than 10% of patients)

Gastrointestinal: nausea, constipation, diarrhea, vomiting, swallowing difficulties

General: feeling tired, fever, weight loss
Metabolism and Nutrition: decreased appetite
Endocrine: hypothyroidism (underactive thyroid)
Infections: upper respiratory tract infection
Musculoskeletal and Connective Tissue: pain in muscles, pain in the neck
Skin and Subcutaneous Tissue: rash, hair loss, swelling of the lining of the mouth, nose, eyes, throat, intestines, or vagina, and mouth sores
Respiratory, Thoracic and Mediastinal: cough, shortness of breath
Nervous System: inflammation of the nerves that may cause pain, weakness, and paralysis in the arms and legs, headache, dizziness, trouble sleeping

Very common side effects of KEYTRUDA when given with axitinib include:

(reported in greater than 20% of patients)

Gastrointestinal: diarrhea, nausea, constipation

General: feeling tired or weak

Vascular: high blood pressure

Hepatobiliary: liver problems

Endocrine: low levels of thyroid hormone

Metabolism and Nutrition: decreased appetite

Skin and Subcutaneous Tissue: blisters or rash on the palms of your hands and soles of your feet, mouth sores or swelling of the lining of the mouth, nose, eyes, throat, intestines, or vagina, rash.

Respiratory, Thoracic and Mediastinal: hoarseness, cough

Very common side effects of KEYTRUDA when given with lenvatinib include:

(reported in greater than 20% of patients)

General: feeling tired, weight loss

Gastrointestinal: diarrhea, mouth sores, nausea, stomach area (abdominal) pain, vomiting, constipation

Musculoskeletal and Connective Tissue: joint and muscle pain

Endocrine: low levels of thyroid hormone

Vascular: high blood pressure, bleeding

Metabolism and Nutrition: decreased appetite

Skin and Subcutaneous Tissue: rash, blisters or rash on the palms of your hands and soles of your feet

Respiratory, Thoracic and Mediastinal: hoarseness

Renal and Urinary: protein in your urine, kidney problems

Infections: urinary tract infection

Hepatobiliary: liver problems

Nervous System: headache

These are not all the possible side effects of **KEYTRUDA**. For more information, ask your doctor or pharmacist.

Tell your doctor if you have any side effect that bothers you or that does not go away.

If a side effect appears, if any of the side effects gets worse or if you suffer from a side effect not mentioned in this leaflet, consult your doctor.

Reporting side effects

Side effects can be reported to the Ministry of Health by clicking the link “reporting side effects due to medical treatment” located in the home page of the Ministry of Health web site (www.health.gov.il) directing to the on line form for side effects reporting, or by logging on the following link:

<https://sideeffects.health.gov.il>

5. HOW TO STORE KEYTRUDA?

- Avoid Poisoning! This medicine and any other medicine must be stored in a safe place out of the reach and sight of children and/or infants, in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by a doctor!
- Do not use **KEYTRUDA** after the expiry date (exp. date) that appears on the packaging. The expiry date refers to the last day of the indicated month.
- **Storage conditions:**
KEYTRUDA 100 mg/4 mL concentrate for solution for Intravenous Infusion: store vials under refrigeration at 2°C to 8°C in original carton to protect from light. Do not freeze. Do not shake.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

6.1 What KEYTRUDA contains

Active ingredient: pembrolizumab.

Inactive ingredients:

KEYTRUDA 100 mg/4 mL concentrate for solution for Intravenous Infusion: Water for injection, sucrose, L-histidine, polysorbate 80.

6.2 What KEYTRUDA looks like and contents of the package

KEYTRUDA 100 mg/4 mL concentrate for solution for Intravenous Infusion is a clear to slightly opalescent, colorless to slightly yellow solution.

KEYTRUDA 100 mg/4 mL concentrate for solution for Intravenous Infusion is supplied in a carton containing one 100 mg/4 mL (25 mg/mL) single-use vial.

6.3 Marketing authorization holder and address

Merck Sharp & Dohme (Israel-1996) Company Ltd., P.O.Box 7121, Petah-Tikva 49170.

6.4 Manufacturer

Merck Sharp & Dohme Corp., New-Jersey, USA.

Revised in April 2022 according to MoH guidelines.

Registration number of the medicine listed in the National Drug Registry of the Ministry of Health:
154.38.34448