רופא/ה יקר/ה,
רוקח/ת יקר/ה,

מרץ 2018

הנדון: KEYTRUDA® 50 mg, KEYTRUDA® 100 mg/4 mL
קיטרודה 50 מ"ג , קיטרודה 100 מ"ג/ 4 מ"ל
תוספת התוויות-
Urothelial Carcinoma: Cisplatin Ineligible Patients, Microsatellite Instability-High (MSI-H) Cancer, Gastric Cancer

Dosage form:
Keytruda 50 mg-Powder for Solution for Intravenous Infusion
Keytruda 100 mg/4 ml-Concentrate for Solution for Intravenous Infusion

Composition:
Keytruda 50 mg- pembrolizumab 50 mg/vial
Keytruda 100 mg/4 ml- pembrolizumab 100 mg/4 ml

חברת מרק שארפ ודוהם ישראל (MSD ישראל) שמחה לעדכן כי משרד הבריאות אישר תוספת התוויות עבור התכשיר KEYTRUDA® וכן עדכונים בעלון לרופא.

עדכונים מהותיים שבוצעו בעלון לרופא (טקסט שהוסף מסומן בקו תחתון, טקסט שנמחק מסומן בקו חוצה):

1. INDICATIONS AND USAGE

1.1 Melanoma
KEYTRUDA (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*.

1.2 Non-Small Cell Lung Cancer
KEYTRUDA is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 [Tumor Proportion Score (TPS) ≥50%)] as determined by a validated test. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on or after platinum-containing chemotherapy and an approved therapy for these aberrations prior to receiving KEYTRUDA *[see Clinical Studies (14.2)]*.

KEYTRYDA is indicated for the treatment of patients with advanced non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by a validated test, with disease progression on or after platinum containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on approved therapy for these aberrations prior to receiving KEYTRUDA *[see Clinical Studies (14.2)]*.

1.3 Head and Neck Cancer
KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy *[see Clinical Studies (14.3)]*.

1.4 Classical Hodgkin Lymphoma
KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after 3 or more prior lines of therapy *[see Clinical Studies (14.4)]*.

1.5 Urothelial Carcinoma
KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy [see Clinical Studies (14.5)].
KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy *[see Clinical Studies (14.5)].*

1.6 Microsatellite Instability-High Cancer
KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient

- solid tumors that have progressed following prior systemic treatment and who have no satisfactory alternative treatment options, or

- colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan *[see Clinical Studies (14.6)]*.

Limitation of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.

1.7 Gastric Cancer
KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by a validated test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy *[see Clinical Studies (14.7)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for Treatment of NSCLC or Gastric Cancer
Select patients for treatment of metastatic NSCLC with KEYTRUDA based on the presence of positive PD-L1 expression *[see Clinical Studies (14.2)]*.
Select patients for treatment of metastatic gastric cancer with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression *[see Clinical Studies (14.7)]*. If PD-L1 expression is not detected in an archival gastric cancer specimen, evaluate the feasibility of obtaining a tumor biopsy for PD-L1 testing.
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2.6 Recommended Dosage for Urothelial Carcinoma
The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression *[see Clinical Studies (14.5)]*.

2.7 Recommended Dosage for MSI-H Cancer
The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression *[see Clinical Studies (14.6)]*.

The recommended dose of KEYTRUDA in children is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

2.8 Recommended Dosage for Gastric Cancer
The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression *[see Clinical Studies (14.7)]*.

5 Warnings and Precautions
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5.10 Increased Mortality in Patients with Multiple Myeloma when KEYTRUDA is Added to a Thalidomide Analogue and Dexamethasone
In two randomized clinical trials in patients with multiple myeloma, the addition of KEYTRUDA to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

6 Adverse Reactions
6.1 Clinical Trials Experience
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Urothelial Carcinoma
Cisplatin Ineligible Patients with Urothelial Carcinoma
The safety of KEYTRUDA was investigated in Study KEYNOTE-052, a single-arm trial that enrolled 370 patients with locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy. Patients with autoimmune disease or medical conditions that required systemic corticosteroids or other immunosuppressive medications were ineligible. Patients received KEYTRUDA

200 mg every 3 weeks until unacceptable toxicity or either radiographic or clinical disease progression. The median duration of exposure to KEYTRUDA was 2.8 months (range: 1 day to 15.8 months).

The most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, decreased appetite, constipation, rash and diarrhea. KEYTRUDA was discontinued due to adverse reactions in 11% of patients. Eighteen patients (5%) died from causes other than disease progression. Five patients (1.4%) who were treated with KEYTRUDA experienced sepsis which led to death, and three patients (0.8%) experienced pneumonia which led to death. Adverse reactions leading to interruption of KEYTRUDA occurred in 22% of patients; the most common (≥1%) were liver enzyme increase, diarrhea, urinary tract infection, acute kidney injury, fatigue, joint pain, and pneumonia. Serious adverse reactions occurred in 42% of patients. The most frequent serious adverse reactions (≥2%) were urinary tract infection, hematuria, acute kidney injury, pneumonia, and urosepsis.

Immune-related adverse reactions that required systemic glucocorticoids occurred in 8% of patients, use of hormonal supplementation due to an immune-related adverse reaction occurred in 8% of patients, and 5% of patients required at least one steroid dose ≥40 mg oral prednisone equivalent.

Table 9 summarizes the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA.

Table 9: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-052

	KEYTRUDA 200 mg every 3 weeks N=370	
Adverse Reaction	**All Grades* (%)**	**Grades 3 – 4 (%)**
All Adverse Reactions	96	49
Blood and Lymphatic System Disorders		
Anemia	17	7
Gastrointestinal Disorders		
Constipation	21	1.1
Diarrhea†	20	2.4
Nausea	18	1.1
Abdominal pain‡	18	2.7
Elevated LFTs§	13	3.5
Vomiting	12	0
General Disorders and Administration Site Conditions		
Fatigue¶	38	6
Pyrexia	11	0.5
Weight decreased	10	0
Infections and Infestations		
Urinary tract infection	19	9
Metabolism and Nutrition Disorders		
Decreased appetite	22	1.6
Hyponatremia	10	4.1
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain#	24	4.9
Arthralgia	10	1.1
Renal and Urinary Disorders		
Blood creatinine increased	11	1.1
Hematuria	13	3.0
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	14	0
Dyspnea	11	0.5
Skin and Subcutaneous Tissue Disorders		
Rashᵖ	21	0.5
Pruritis	19	0.3
Edema peripheral	14	1.1

* Graded per NCI CTCAE v4.0
† Includes diarrhea, colitis, enterocolitis, gastroenteritis, frequent bowel movements
‡ Includes abdominal pain, pelvic pain, flank pain, abdominal pain lower, tumor pain, bladder pain, hepatic pain, suprapubic pain, abdominal discomfort, abdominal pain upper
§ Includes autoimmune hepatitis, hepatitis, hepatitis toxic, liver injury, transaminases increased, hyperbilirubinemia, blood bilirubin increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzymes increased, liver function tests increased
¶ Includes fatigue, asthenia
# Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity, spinal pain
ᵖ Includes dermatitis, dermatitis bullous, eczema, erythema, rash, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin reaction, dermatitis acneiform, seborrheic dermatitis, palmar-plantar erythrodysesthesia syndrome, rash generalized

Gastric Cancer

Among the 259 patients with gastric cancer enrolled in Study KEYNOTE-059, the median duration of exposure to KEYTRUDA was 2.1 months (range: 1 day to 21.4 months). Patients with autoimmune disease or a medical

condition that required immunosuppression or with clinical evidence of ascites by physical exam were ineligible.
Adverse reactions occurring in patients with gastric cancer were similar to those occurring in patients with melanoma or NSCLC.

12.3 Pharmacokinetics
Updated population PK analysis data- see leaflet.

14 Clinical Studies
Added data for Urothelial Carcinoma- Cisplatin Ineligible Patients, Microsatellite Instability-High Cancer and Gastric Cancer- see leaflet.

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפס על ידי פניה לבעל הרישום, חברת MSD ישראל, בטלפון 09-9533333.

KEYTRUDA מופצת ע"י חברת נובולוג בע"מ.

בברכה,

דורית מאורי
רוקחת ממונה
MSD ישראל

Refrences:
Israeli approved PC01/2018

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