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- Classical Hodgkin Lymphoma ו- Urothelial Carcinoma

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 להודיע כי משרד הבריאות אישר תוספת התוויות עבור התכשיר KEYTRUDA® וכן עדכונים בעלונים לרופא ולצרכן.

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 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)]*.

2 DOSAGE AND ADMINISTRATION

2.5 Recommended Dosage for cHL
The recommended dose of KEYTRUDA in adults 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 (14.4)]*.

The recommended dose of KEYTRUDA in pediatric patients 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.

2.6 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 Dose Modifications

Withhold KEYTRUDA for any of the following: Grade 4 hematological toxicity in cHL patients…
Permanently discontinue KEYTRUDA for any of the following: Any life-threatening adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy, or hematological toxicity in patients with cHL)…

5 WARNINGS AND PRECAUTIONS

~~**5.6 Severe Skin Reactions**~~

~~Immune-mediated severe skin reactions have been reported in patients treated with KEYTRUDA. Monitor patients for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids *[see Dosage and Administration (2.5)]*.~~
~~Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients treated with KEYTRUDA. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA *[see Dosage and Administration (2.5)]*.~~

5.6 Immune-Mediated Skin Adverse Reactions

Immune-mediated rashes, including SJS, TEN (some cases with fatal outcome), exfoliative dermatitis, and bullous pemphigoid, can occur. Monitor patients for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA. *[See Dosage and Administration (2.7).]*

5.7 Other Immune-Mediated Adverse Reactions

KEYTRUDA can cause other clinically important immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system…

The following clinically significant, immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 2799 patients treated with KEYTRUDA: arthritis (1.5%), uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, and partial seizures arising in a patient with inflammatory foci in brain parenchyma. In addition, myelitis and myocarditis were reported in other clinical trials, including cHL, and post-marketing use…

5.8 Infusion-Related Reactions

KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA…

5.9 Complications of Allogeneic HSCT after KEYTRUDA

Immune-mediated complications, including fatal events, occurred in patients who underwent allogeneic hematopoietic stem cell transplantation (HSCT) after being treated with KEYTRUDA. Of 23 patients with cHL who proceeded to allogeneic HSCT after treatment with KEYTRUDA on any trial, 6 patients (26%) developed graft-versus-host-disease (GVHD), one of which was fatal, and 2 patients (9%) developed severe hepatic veno-occlusive disease (VOD) after reduced-intensity conditioning, one of which was fatal.
Cases of fatal hyperacute GVHD after allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor blocking antibody before transplantation. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT. Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic VOD, and other immunemediated adverse reactions, and intervene promptly.

6 ADVERSE REACTIONS

cHL

Among the 210 patients with cHL enrolled in Study KEYNOTE-087 *[see Clinical Studies (14.4)]*, the median duration of exposure to KEYTRUDA was 8.4 months (range: 1 day to 15.2 months). KEYTRUDA was discontinued due to adverse reactions in 5% of patients, and treatment was interrupted due to adverse reactions in 26%. Fifteen percent (15%) of patients had an adverse reaction requiring systemic corticosteroid therapy. Serious adverse reactions occurred in 16% of patients. The most frequent serious adverse reactions (≥1%) included pneumonia, pneumonitis, pyrexia, dyspnea, graft versus host disease and herpes zoster. Two patients died from causes other than disease progression; one from GVHD after subsequent allogeneic HSCT and one from septic shock.

Table 7 summarizes the adverse reactions that occurred in at least 10% of patients treated with KEYTRUDA.

Table 7: Adverse Reactions in ≥10% of Patients with cHL in KEYNOTE-087

	KEYTRUDA 200 mg every 3 weeks N=210	
Adverse Reaction	All Grades* (%)	Grade 3 (%)
General Disorders and Administration Site Conditions		
Fatigue[†]	26	1.0
Pyrexia	24	1.0
Respiratory, Thoracic and Mediastinal Disorders		
Cough[‡]	24	0.5
Dyspnea[§]	11	1.0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[¶]	21	1.0
Arthralgia	10	0.5
Gastrointestinal Disorders		
Diarrhea[#]	20	1.4
Vomiting	15	0
Nausea	13	0
Skin and Subcutaneous Tissue Disorders		
Rash[Þ]	20	0.5
Pruritus	11	0
Endocrine Disorders		
Hypothyroidism	14	0.5
Infections and Infestations		
Upper respiratory tract infection	13	0
Nervous System Disorders		
Headache	11	0.5
Peripheral neuropathy[β]	10	0

* Graded per NCI CTCAE v4.0
† Includes fatigue, asthenia
‡ Includes cough, productive cough
§ Includes dyspnea, dyspnea exertional, wheezing
¶ Includes back pain, myalgia, bone pain, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain
# Includes diarrhea, gastroenteritis, colitis, enterocolitis
Þ Includes rash, rash maculo-papular, drug eruption, eczema, eczema asteatotic, dermatitis, dermatitis acneiform, dermatitis contact, rash erythematous, rash macular, rash papular, rash pruritic, seborrhoeic dermatitis, dermatitis psoriasiform
β Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paresthesia, dysesthesia, polyneuropathy

Other clinically important adverse reactions that occurred in less than 10% of patients on KEYNOTE-087 included infusion reactions (9%), hyperthyroidism (3%), pneumonitis (3%), uveitis and myositis (1% each), myelitis and myocarditis (0.5% each).

Table 8: Selected Laboratory Abnormalities Worsened from Baseline Occurring in ≥15% of cHL Patients Receiving KEYTRUDA in KEYNOTE-087

	KEYTRUDA 200 mg every 3 weeks	
Laboratory Test*	All Grades[†] (%)	Grade 3-4 (%)
Chemistry		
Hypertransaminasemia[‡]	34%	2%
Alkaline phosphatase increased	17%	0%
Creatinine increased	15%	0.5%
Hematology		
Anemia	30%	6%
Thrombocytopenia	27%	4%
Neutropenia	24%	7%

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 208 to 209 patients)
† Graded per NCI CTCAE v4.0
‡ Includes elevation of AST or ALT

Hyperbilirubinemia occurred in less than 15% of patients on KEYNOTE-087 (10% all Grades, 2.4% Grade 3-4).

Urothelial Carcinoma

Previously Treated Urothelial Carcinoma

The safety of KEYTRUDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma with disease progression following platinum-containing chemotherapy was investigated in Study KEYNOTE-045. KEYNOTE-045 was a multicenter, open-label, randomized (1:1), active-controlled trial in which 266 patients received KEYTRUDA 200 mg every 3 weeks or investigator's choice of chemotherapy (n=255), consisting of paclitaxel (n=84), docetaxel (n=84) or vinflunine (n=87) *[see Clinical Studies (14.5)]*. Patients with autoimmune disease or a medical condition that required systemic corticosteroids or other immunosuppressive medications were ineligible. The median duration of exposure was 3.5 months (range: 1 day to 20 months) in patients who received KEYTRUDA and 1.5 months (range: 1 day to 14 months) in patients who received chemotherapy.

KEYTRUDA was discontinued due to adverse reactions in 8% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.9%). Adverse reactions leading to interruption of KEYTRUDA occurred in 20% of patients; the most common (≥1%) were urinary tract infection (1.5%), diarrhea (1.5%), and colitis (1.1%). The most common adverse reactions (occurring in at least 20% of patients who received KEYTRUDA) were fatigue, musculoskeletal pain, pruritus, decreased appetite, nausea and rash. Serious adverse reactions occurred in 39% of KEYTRUDA-treated patients. The most frequent serious adverse reactions (≥2%) in KEYTRUDA-treated patients were urinary tract infection, pneumonia, anemia, and pneumonitis.

Table 9 summarizes the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA. Table 10 summarizes the incidence of laboratory abnormalities that occurred in at least 20% of patients receiving KEYTRUDA.

Table 9: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-045

	KEYTRUDA 200 mg every 3 weeks n=266		Chemotherapy* n=255	
Adverse Reaction	**All Grades† (%)**	**Grade 3-4 (%)**	**All Grades† (%)**	**Grade 3-4 (%)**
Gastrointestinal Disorders				
Nausea	21	1.1	29	1.6
Constipation	19	1.1	32	3.1
Diarrhea‡	18	2.3	19	1.6
Vomiting	15	0.4	13	0.4
Abdominal pain	13	1.1	13	2.7
General Disorders and Administration Site Conditions				
Fatigue§	38	4.5	56	11
Pyrexia	14	0.8	13	1.2
Infections and Infestations				
Urinary tract infection	15	4.9	14	4.3
Metabolism and Nutrition Disorders				
Decreased appetite	21	3.8	21	1.2
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain¶	32	3.0	27	2.0
Renal and Urinary Disorders				
Hematuria#	12	2.3	8	1.6
Respiratory, Thoracic and Mediastinal Disorders				
Cough Þ	15	0.4	9	0
Dyspnea ß	14	1.9	12	1.2
Skin and Subcutaneous Tissue Disorders				
Pruritus	23	0	6	0.4
Rash[a]	20	0.4	13	0.4

* Chemotherapy: paclitaxel, docetaxel, or vinflunine

† Graded per NCI CTCAE v4.0

‡ Includes diarrhea, gastroenteritis, colitis, enterocolitis

§ Includes asthenia, fatigue, malaise lethargy

¶ Includes back pain, myalgia, bone pain, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain

Includes blood urine present, hematuria, chromaturia

Þ Includes cough, productive cough

ß Includes dyspnea, dyspnea exertional, wheezing

[a] Includes rash maculo-papular, rash genital rash, rash erythematous, rash papular, rash pruritic, rash pustular, erythema, drug eruption, eczema, eczema asteatotic, dermatitis contact, dermatitis acneiform, dermatitis, seborrhoeic keratosis, lichenoid keratosis

Table 10: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Urothelial Carcinoma Patients Receiving KEYTRUDA in KEYNOTE-045

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks		Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Chemistry				
Glucose increased	52	8	60	7
Hemoglobin decreased	52	13	68	18
Lymphocytes decreased	45	15	53	25
Albumin decreased	43	1.7	50	3.8
Sodium decreased	37	9	47	13
Alkaline phosphatase increased	37	7	33	4.9
Creatinine increased	35	4.4	28	2.9
Phosphate decreased	29	8	34	14
Aspartate aminotransferase increased	28	4.1	20	2.5
Potassium increased	28	0.8	27	6
Calcium decreased	26	1.6	34	2.1

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 240 to 248 patients) and chemotherapy (range: 238 to 244 patients); phosphate decreased: KEYTRUDA n=232 and chemotherapy n=222.

† Graded per NCI CTCAE v4.0

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

~~Safety and effectiveness of KEYTRUDA have not been established in pediatric patients.~~

There is limited experience with KEYTRUDA in pediatric patients. In a study, 40 pediatric patients (16 children ages 2 years to less than 12 years and 24 adolescents ages 12 years to 18 years) with advanced melanoma, lymphoma, or PD-L1 positive advanced, relapsed, or refractory solid tumors were administered KEYTRUDA 2 mg/kg every 3 weeks. Patients received KEYTRUDA for a median of 3 doses (range: 1-17 doses), with 34 patients (85%) receiving KEYTRUDA for 2 doses or more. The concentrations of pembrolizumab in pediatric patients were comparable to those observed in adult patients at the same dose regimen of 2 mg/kg every 3 weeks. The safety profile in these pediatric patients was similar to that seen in adults treated with pembrolizumab; toxicities that occurred at a higher rate (≥15% difference) in pediatric patients when compared to adults under 65 years of age were fatigue (45%), vomiting (38%), abdominal pain (28%), hypertransaminasemia (28%) and hyponatremia (18%). Efficacy for pediatric patients with cHL cancer is extrapolated from the results in the respective adult populations *[see Clinical Studies (14.4)].*

8.5 Geriatric Use

Of ~~3145~~ 3991 patients with melanoma, NSCLC, HNSCC, cHL or urothelial carcinoma who were treated with KEYTRUDA in clinical studies, ~~43~~ 46% were 65 years and over and ~~12~~ 16% were 75 years and over.

12 CLINICAL PHARMACOLOGY

Pembrolizumab concentrations with weight-based dosing at 2 mg/kg every 3 weeks in pediatric patients (2 to 17 years) are comparable to those of adults at the same dose.

14 CLINICAL STUDIES

Updated efficacy data for Melanoma- see leaflet.
Added data for Classical Hodgkin Lymphoma and Urothelial Carcinoma- see leaflet.

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

1. מהי קיטרודה ולמה היא משמשת?

- סוג של סרטן הנקרא לימפומת הודג'קין קלאסית (cHL) במבוגרים וילדים כאשר:
  - ניסית טיפול והוא אינו עבד **או**
  - ה- cHL שלך חזרה לאחר שקיבלת 3 או יותר סוגים של טיפול.

- סוג של סרטן שלפוחית השתן ודרכי השתן (urothelial carcinoma). ניתן להשתמש ב**קיטרודה** כאשר סרטן שלפוחית השתן או דרכי השתן שלך:
  - התפשט או שאין אפשרות להסירו על ידי ניתוח (סרטן מתקדם של דרכי השתן) **ו**
  - קיבלת כימותרפיה המכילה פלטינום, והיא לא פעלה או אינה פועלת יותר.

~~לא ידוע אם **קיטרודה** בטוחה ויעילה בילדים מתחת לגיל 18 שנים ולכן אינה מיועדת לשימוש באונקולוסיה זו.~~

4. תופעות לוואי

~~**סימנים ותסמינים של**~~ **בעיות בעור.** סימנים של בעיות בעור יכולים לכלול:
פריחה; גרוד; שלפוחיות, קילוף או פצעים בעור; פצעים או כיבים כואבים בפה שלך או ~~בדופן האף~~ באף, בגרון או באזור אברי המין שלך.

דחייה של איברים מושתלים. אנשים שעברו השתלת איברים עלולים להיות בעלי סיכון מוגבר לדחיית האיבר המושתל במידה והם מטופלים בקיטרודה. על הרופא שלך לומר לך על אילו סימנים ותסמינים עליך לדווח, והוא יבצע מעקב, בהתאם לסוג השתלת האיברים שהיתה לך.

סיבוכים של השתלת תאי גזע מתורם (אלוגנאית) לאחר טיפול בקיטרודה. סיבוכים אלו עלולים להיות חמורים ולהוביל למוות. אם עברת השתלת תאי גזע אלוגנאית, הרופא שלך יבצע מעקב לזיהוי סימנים המעידים על סיבוכים.

תופעות לוואי שכיחות של **קיטרודה** כוללות: הרגשת עייפות, גרוד, שלשול, ירידה בתיאבון, פריחה, חום, שיעול, קוצר נשימה, כאב בשרירים, עצמות או מפרקים, עצירות, ובחילה.

בילדים, הרגשת עייפות, הקאות וכאב באזור הבטן, עלייה ברמות אנזימי הכבד וירידה ברמות המלח בדם (נתרן) הינם שכיחים יותר מאשר במבוגרים.

קיימים עדכונים נוספים בעלונים אשר אינם מהותיים ואינם נכללים בהודעה זו.

למידע מלא ולהוראות מתן מפורטות, יש לעיין בעלונים לרופא ולצרכן המאושרים על ידי משרד הבריאות.

העלונים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים 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 PC10/2017
Israeli approved PPI 10/2017

ONCO-1243096-0000