רופא/ה יקר/ה,
רוקח/ת יקר/ה,

דצמבר 2019

הנדון: KEYTRUDA® 50 mg, KEYTRUDA® 100 mg/4 mL
קיטרודה 50 מ"ג , קיטרודה 100 מ"ג/ 4 מ"ל

Dosage form and Composition:
Keytruda 50 mg- pembrolizumab 50 mg/vial; Powder for Solution for Intravenous Infusion
Keytruda 100 mg/4 ml- pembrolizumab 100 mg/4 ml; Concentrate for Solution for Intravenous Infusion

חברת מרק שארפ ודוהם ישראל (MSD ישראל) מבקשת ליידע על עדכון העלון לרופא של התכשיר KEYTRUDA להכללת התוויות נוספות שאושרו וכן עדכונים אחרים כמפורט להלן.

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

1 INDICATIONS AND USAGE **עדכונים בפרק:**

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1.2 Non-Small Cell Lung Cancer

KEYTRUDA, in combination with pemetrexed and carboplatin, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC) negative for EGFR or ALK genomic tumor aberrations *[see Clinical Studies (14.2)]*.

KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of patients with metastatic squamous NSCLC *[see Clinical Studies (14.2)]*.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic 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)]*.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with advanced 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)]*.

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1.5 Primary Mediastinal large B-Cell Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy. *[see Clinical Studies (14.5)]*.

Limitation of Use: KEYTRUDA is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

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1.9 Cervical Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by a validated test *[see Clinical Studies (14.9)]*.

2 DOSAGE AND ADMINISTRATION **עדכונים בפרק:**

2.1 Patient Selection for Treatment of NSCLC, Gastric Cancer, or Cervical Cancer

Select patients for treatment with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression in:

- metastatic NSCLC *[see Clinical Studies (14.2)]*.
- metastatic gastric cancer *[see Clinical Studies (14.8)]*. 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.
- recurrent or metastatic cervical cancer *[see Clinical Studies (14.9)]*.

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2.3 Recommended Dosage for NSCLC

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 (14.2)]*.

When administering KEYTRUDA in combination with chemotherapy, KEYTRUDA should be administered prior to chemotherapy when given on the same day *[see Clinical Studies (14.2)]*. See also the Prescribing Information for the chemotherapy agents administered in combination with KEYTRUDA, as appropriate.

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2.6 Recommended Dosage for PMBCL

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 (14.5)]*.

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.

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2.10 Recommended Dosage for Cervical 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 (14.9)].

2.11 Dose Modifications

Withhold KEYTRUDA for any of the following:

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- Grade 4 hematological toxicity in cHL or PMBCL patients

Permanently discontinue KEYTRUDA for any of the following:

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- Any life-threatening adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy, or hematological toxicity in patients with cHL or PMBCL)

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5 Warnings and Precautions **עדכונים בפרק:**

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5.5 Immune-Mediated Nephritis and Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Monitor patients for changes in renal function. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater nephritis. Withhold KEYTRUDA for moderate (Grade 2), and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) nephritis *[see Dosage and Administration (2.11) and Adverse Reactions (6.1)]*.

Nephritis occurred in 9 (0.3%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), Grade 3 (0.1%), and Grade 4 (<0.1%) nephritis. The median time to onset was 5.1 months (range: 12 days to 12.8 months), and the median duration was 3.3 months (range: 12 days to 8.9+ months). Eight (89%) of the 9 patients received systemic corticosteroids, with 7 of the 8 receiving high-dose corticosteroids for a median duration of 15 days (range: 3 days to 4.0 months) followed by a corticosteroid taper. Nephritis led to discontinuation of KEYTRUDA in 3 (0.1%) patients. Nephritis resolved in 5 (56%) of the 9 patients. Nephritis occurred in 1.7% of 405 patients receiving KEYTRUDA in combination with pemetrexed and platinum in the KEYNOTE-189 study, including Grade 3 (1%) and Grade 4 (0.5%) nephritis. The median time to onset was 3.2 months (range: 16 days to 11.1 months) and the duration ranged from 1.6 to 16.8+ months. Six (86%) of the 7 patients received systemic corticosteroids, with all 6 receiving high-dose corticosteroids for a median duration of 3 days (range: 1 to 17 days) followed by a corticosteroid taper. Nephritis led to discontinuation of KEYTRUDA in 5 (1.2%) patients. Nephritis resolved in 2 (29%) of the 7 patients.

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5.7 Other Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue in patients receiving KEYTRUDA. While immune-mediated adverse reactions usually occur during treatment with PD-1/PD-L1 blocking antibodies, they may occur after discontinuation of treatment.

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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~~ sarcoidosis and encephalitis. In addition, myelitis and myocarditis were reported in other clinical trials, including cHL, and post-marketing use.

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5.9 Complications of Allogeneic HSCT

Allogeneic HSCT after treatment with 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 immune-mediated adverse reactions, and intervene promptly.

Allogeneic HSCT prior to treatment with KEYTRUDA

In patients with a history of allogeneic HSCT, acute GVHD, including fatal GVHD, has been reported after treatment with KEYTRUDA. Patients who experienced GVHD after their transplant procedure may be at increased risk for GVHD after treatment with KEYTRUDA. Consider the benefit of treatment with KEYTRUDA versus the risk of possible GVHD in patients with a history of allogeneic HSCT.

6 Adverse Reactions **עדכונים בפרק:**

6.1 Clinical Trials Experience

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NSCLC

First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy

The safety of KEYTRUDA in combination with pemetrexed and investigator's choice of platinum (either carboplatin or cisplatin) was investigated in Study KEYNOTE-189, a multicenter, double-blind, randomized (2:1), active-controlled trial in patients with previously untreated, metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations. A total of 607 patients received KEYTRUDA 200 mg, pemetrexed and platinum every 3 weeks for 4 cycles followed by KEYTRUDA and pemetrexed (n=405) or placebo, pemetrexed, and platinum every 3 weeks for 4 cycles followed by placebo and pemetrexed (n=202). Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible *[see Clinical Studies (14.2)]*.

The median duration of exposure to KEYTRUDA 200 mg every 3 weeks was 7.2 months (range: 1 day to 20.1 months). Sixty percent of patients in the KEYTRUDA arm were exposed to KEYTRUDA for ≥6 months. Seventy-two percent of patients received carboplatin. The study population characteristics were: median age of 64 years (range: 34 to 84), 49% age 65 years or older, 59% male, 94% White and 3% Asian, and 18% with history of brain metastases at baseline.

KEYTRUDA was discontinued for adverse reactions in 20% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (3%) and acute kidney injury (2%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 53% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were neutropenia (13%), asthenia/fatigue (7%), anemia (7%), thrombocytopenia (5%), diarrhea (4%), pneumonia (4%), increased blood creatinine (3%), dyspnea (2%), febrile neutropenia (2%), upper respiratory tract infection (2%), increased ALT (2%), and pyrexia (2%).

Table 5 summarizes the adverse reactions that occurred in at least 20% of patients treated with KEYTRUDA.
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Table 6 summarizes the laboratory abnormalities that worsened from baseline in at least 20% of patients treated with KEYTRUDA
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First-line treatment of metastatic squamous NSCLC with carboplatin and either paclitaxel or nab-paclitaxel chemotherapy

The safety of KEYTRUDA in combination with carboplatin and investigator's choice of either paclitaxel or nab-paclitaxel was investigated in Study KEYNOTE-407, a multicenter, double-blind, randomized (1:1), placebo-controlled trial in 558 patients with previously untreated, metastatic squamous NSCLC. Safety data are available for the first 203 patients who received KEYTRUDA and chemotherapy (n=101) or placebo and chemotherapy (n=102). Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible *[see Clinical Studies (14.2)]*.

The median duration of exposure to KEYTRUDA was 7 months (range: 1 day to 12 months). Sixty-one percent of patients in the KEYTRUDA arm were exposed to KEYTRUDA for ≥6 months. A total of 139 of 203 patients (68%) received paclitaxel and 64 patients (32%) received nab-paclitaxel in combination with carboplatin. The study population characteristics were: median age of 65 years (range: 40 to 83); 52% age 65 or older; 78% male; 83% White; and 9% with history of brain metastases.

KEYTRUDA was discontinued for adverse reactions in 15% of patients, with no single type of adverse reaction accounting for the majority. Adverse reactions leading to interruption of KEYTRUDA occurred in 43% of patients; the most common (≥2%) were thrombocytopenia (20%), neutropenia (11%), anemia (6%), asthenia (2%), and diarrhea (2%). The most frequent (≥2%) serious adverse reactions were febrile neutropenia (6%), pneumonia (6%), and urinary tract infection (3%).

The adverse reactions observed in KEYNOTE-407 were similar to those observed in KEYNOTE-189 with the exception that increased incidences of alopecia (47% vs. 36%) and peripheral neuropathy (31% vs. 25%) were observed in the KEYTRUDA and chemotherapy arm compared to the placebo and chemotherapy arm in KEYNOTE-407.
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PMBCL
Among the 53 patients with PMBCL treated in KEYNOTE-170 [see Clinical Studies (14.5)], the median duration of exposure to KEYTRUDA was 3.5 months (range: 1 day to 22.8 months). KEYTRUDA was discontinued due to adverse reactions in 8% of patients, and treatment was interrupted due to adverse reactions in 15%. Twenty-five percent of patients had an adverse reaction requiring systemic corticosteroid therapy. Serious adverse reactions occurred in 26% of patients, and included arrhythmia (4%), cardiac tamponade (2%), myocardial infarction (2%), pericardial effusion (2%), and pericarditis (2%). Six (11%) patients died within 30 days of start of treatment.

Table 11 summarizes the adverse reactions that occurred in at least 10% of patients treated with KEYTRUDA.
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Table 12 summarizes the incidence of laboratory abnormalities that occurred in at least 15% of patients receiving KEYTRUDA.
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Other clinically important adverse reactions that occurred in less than 10% of patients in KEYNOTE-170 included hypothyroidism (8%), hyperthyroidism and pericarditis (4% each), and thyroiditis, pericardial effusion, pneumonitis, arthritis and acute kidney injury (2% each).
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Cervical Cancer
Among the 98 patients with cervical cancer enrolled in Cohort E of Study KEYNOTE-158, the median duration of exposure to KEYTRUDA was 2.9 months (range: 1 day to 22.1 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

KEYTRUDA was discontinued due to adverse reactions in 8% of patients. Serious adverse reactions occurred in 39% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported included anemia (7%), fistula (4.1%), hemorrhage (4.1%), and infections [except UTIs] (4.1%).

Table 16 summarizes the adverse reactions occurring in at least 10% of patients receiving KEYTRUDA.
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Table 17 summarizes the laboratory abnormalities that occurred in at least 20% of patients receiving KEYTRUDA.
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8.4 Pediatric Use

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Efficacy for pediatric patients with cHL, PMBCL or MSI-H cancers is extrapolated from the results in the respective adult populations *[see Clinical Studies (14.4, 14.5, 14.7)]*.

14 Clinical Studies

נוסף מידע לגבי ההתוויות:

First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy; First-line treatment of metastatic squamous NSCLC with carboplatin and either paclitaxel or nab-paclitaxel chemotherapy; Primary Mediastinal Large B-Cell Lymphoma (PMBCL); Cervical 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 SPC 03/2019