

ינואר 2021

רופא/ה יקר/ה
רוקח/ת יקר/ה,

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

Dosage form and Composition:
Pembrolizumab 100 mg/4 ml; Concentrate for Solution for Intravenous Infusion

חברת מרק שארפ ודוהם (ישראל-1996) בע"מ, (MSD ישראל), מבקשת ליידע על עדכון העלון לרופא ולצרכן של **Keytruda 100mg/4ml** להכללת התוויה נוספת שאושרה 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 THERAPEUTIC INDICATIONS

עדכונים בפרק

1.10 Esophageal Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (CPS≥10) as determined by a validated test, with disease progression after one or more prior lines of systemic therapy.

2 DOSAGE AND ADMINISTRATION

עדכונים בפרק

2.1 Patient Selection for NSCLC, HNSCC, Urothelial Carcinoma, Gastric Cancer, Esophageal 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 esophageal cancer [see Clinical Studies (14.10)].

2.11 Recommended Dosage for Esophageal 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.

עדכונים בפרק **Preparation and Administration** בהוראות ההכנה ואחסון לאחר מיהול:

2.16 Preparation and Administration

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute KEYTRUDA 100 mg/4 mL (concentrated solution) prior to intravenous administration.
- Withdraw the required volume from the vial(s) of KEYTRUDA and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. **Mix diluted solution by gentle inversion. Do not shake.** The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial

Storage of Diluted Solution

The product does not contain a preservative.

From a microbiological point of view, the product, once diluted, should be used immediately. If not used immediately, store the diluted solution from the KEYTRUDA 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the diluted solution, and the duration of infusion.
- Under refrigeration at 2°C to 8°C for no more than **24 96** hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not shake.

Discard after 6 hours at room temperature or after **24 96** hours under refrigeration.

5 WARNINGS AND PRECAUTIONS

עדכונים בפרק

במסגרת עדכון כולל של פרק ה- "Warnings and precautions" בנוגע ל-immune-mediated adverse reactions המיוחסות לתכשירים החוסמים את מסלול PD-1/PD-L1, נוסף המידע המפורט מטה בסעיף 5.1 (מודגש בקו תחתון):

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

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Immune-Mediated Colitis

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Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis.

Immune-Mediated Dermatologic Adverse Reactions

KEYTRUDA can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens Johnson Syndrome, DRESS, and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies.

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Immune-mediated dermatologic adverse reactions occurred in 1.4% (38/2799) of patients receiving KEYTRUDA, including Grade 3 (1%) and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 40% (15/38) of patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions led to permanent discontinuation of KEYTRUDA in 0.1% (2) of patients and withholding of KEYTRUDA in 0.6% (16) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 6% had recurrence of immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 79% of the 38 patients.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received KEYTRUDA or were reported with the use of other PD-1/PD-L1 blocking antibodies.

Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy

Ocular: Uveitis, iritis and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Gastrointestinal: Pancreatitis, to include increases in serum amylase and lipase levels, gastritis, duodenitis

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica

Endocrine: Hypoparathyroidism

Hematologic/Immune: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

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5.6 Esophageal Cancer and Upper Gastrointestinal Hemorrhage

In the KEYTRUDA arm of the esophageal studies after one or more prior lines of therapy, there were 4 fatal events due to upper GI hemorrhage, in patients who had a history of prior radiation therapy to that area. A possible causal association between the events and pembrolizumab use cannot be ruled out.

6 Adverse Reactions

6.1 Clinical Trials Experience

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Esophageal Cancer

Among the 314 patients with esophageal cancer enrolled in KEYNOTE-181 [see Clinical Studies (14.10)] treated with KEYTRUDA, the median duration of exposure to KEYTRUDA was 2.1 months (range: 1 day to 24.4 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with esophageal cancer were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent.

14 Clinical Studies

.Esophageal Cancer תווית לגבי התווית

עדכונים מהותיים שבוצעו בעלון לצרכן (טקסט שהוסף לעלון לרופא מודגש בקו תחתון):
עדכונים בפרק: 1. למה מיועדת קיטרודה?
קיטרודה הינה תרופת מרשם המשמשת לטיפול ב:

- **סרטן ושט הנקרא קרצינומה ממקור תאי קשקש. ניתן להשתמש בקיטרודה כאשר:**
 - **הסרטן שלך חזר או התפשט (סרטן ושט מתקדם).**
 - **הגידול שלך הינו חייבי ל- "PDL-1" וקיבלת סוג אחד או יותר של טיפול והוא לא עבד או אינו עובד יותר.**

סעיף **Instructions for healthcare professionals** - עדכונים בהוראות ההכנה ואחסון לאחר מיהול, זהים לעדכון בעלון לרופא.

ההתוויות המאושרות לתכשיר:

Melanoma

- KEYTRUDA (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma.
- KEYTRUDA is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph node (s) following complete resection.

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.
- KEYTRUDA, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.
- KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 [Tumor Proportion Score (TPS) $\geq 50\%$] 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.
- 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)].

Small Cell Lung Cancer

KEYTRUDA is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy, that have not been previously treated with immunotherapy.

Head and Neck Cancer

- KEYTRUDA, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).
- KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by a validated test.
- KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

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.

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.

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

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 and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 10] as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

- 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.
- KEYTRUDA is indicated for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

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 (dMMR).

- 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.

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

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.

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.

Merkel Cell Carcinoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).

Renal Cell Carcinoma

KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

למידע מלא ולהוראות מתן מפורטות, יש לעיין בעלון לרופא המאשר על ידי משרד הבריאות.

העלונים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום, חברת MSD, בטלפון 09-9533333.

Keytruda 100mg/4ml מופצת ע"י חברת נובולוג בע"מ.

בברכה,
דורית מאורי
רוקחת ממונה
MSD ישראל

References:

Keytruda_100mg_4ml-SPC-01_2021

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