אפריל 2022

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 של Keytruda 100mg/4ml להכללת התווית נוספות שאושרו ועדכונים נוספים.

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

1 THERAPEUTIC INDICATIONS

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1.14 Renal Cell Carcinoma

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

1.15 Endometrial Carcinoma

Keytruda, in combination with lenvatinib, is indicated for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy and who are not candidates for curative surgery or radiation.

2 DOSAGE AND ADMINISTRATION

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2.15 Recommended Dosage for RCC

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks in combination with 5 mg axitinib orally twice daily or in combination with lenvatinib 20 mg orally once daily until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months. When axitinib is used in combination with KEYTRUDA, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer. See also the Prescribing Information for recommended axitinib dosing information.

2.16 Recommended Dosage for Endometrial Carcinoma

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks in combination with lenvatinib 20 mg orally once daily until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months.

2.20 Dose Modifications

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Recommended Dose Modifications for Adverse Reactions for KEYTRUDA in Combination with Lenvatinib
When administering KEYTRUDA in combination with lenvatinib, modify the dosage of one or both drugs. Withhold or discontinue KEYTRUDA as shown in Table 2above. Refer to lenvatinib prescribing information for additional dose modification information.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

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Thyroid Disorders

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Consider frequent monitoring of thyroid function when KEYTRUDA is administered in combination with axitinib or in combination with lenvatinib. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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RCC

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In combination with lenvatinib in the first-line treatment of advanced RCC (KEYNOTE-581)
The safety of KEYTRUDA was evaluated in KEYNOTE-581 [see Clinical Studies 14.14]. Patients received KEYTRUDA 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily (n=352), or lenvatinib 18 mg orally once daily in combination with everolimus 5 mg orally once daily (n=355), or sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks (n=340). The median duration of exposure to the combination therapy of KEYTRUDA and lenvatinib was 17 months (range: 0.1 to 39).
Fatal adverse reactions occurred in 4.3% of patients treated with KEYTRUDA in combination with lenvatinib, including cardio-respiratory arrest (0.9%), sepsis (0.9%), and one case (0.3%) each of arrhythmia, autoimmune hepatitis, dyspnea, hypertensive crisis, increased blood creatinine, multiple organ dysfunction syndrome, myasthenic syndrome, myocarditis, nephritis, pneumonitis, ruptured aneurysm, and subarachnoid hemorrhage.
Serious adverse reactions occurred in 51% of patients receiving KEYTRUDA and lenvatinib. Serious adverse reactions in ≥2% of patients were hemorrhagic events (5%), diarrhea (4%), hypertension (3%), myocardial infarction (3%), pneumonitis (3%), vomiting (3%), acute kidney injury (2%), adrenal insufficiency (2%), dyspnea (2%), and pneumonia (2%).
Permanent discontinuation of either of KEYTRUDA, lenvatinib, or both due to an adverse reaction occurred in 37% of patients receiving KEYTRUDA in combination with Lenvatinib; 29% KEYTRUDA only, 26% lenvatinib only, and 13% both. The most common adverse reactions (≥2%) resulting in permanent discontinuation of KEYTRUDA, lenvatinib, or the combination were pneumonitis (3%), myocardial infarction (3%), hepatotoxicity (3%), acute kidney injury (3%), rash (3%), and diarrhea (2%).
Dose interruptions of KEYTRUDA, lenvatinib, or both due to an adverse reaction occurred in 78% of patients receiving KEYTRUDA in combination with lenvatinib. KEYTRUDA was interrupted in 55% of 48 patients and both drugs were interrupted in 39% of patients. The most common adverse reactions (≥3%) resulting in interruption of KEYTRUDA were diarrhea (10%), hepatotoxicity (8%), fatigue (7%), lipase increased (5%), amylase increased (4%), musculoskeletal pain (3%), hypertension (3%), rash (3%), acute kidney injury (3%), and decreased appetite (3%).
Fifteen percent (15%) of patients treated with KEYTRUDA in lenvatinib received an oral prednisone equivalent to ≥40 mg daily for immune-mediated adverse reaction.
Tables 30 and 31summarize the adverse reactions and laboratory abnormalities, respectively, that occurred in ≥20 of patients treated with KEYTRUDA and lenvatinib in KEYNOTE-581.
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Clinically relevant adverse reactions (<20%) that occurred in patients receiving KEYTRUDA with lenvatinib were myocardial infarction (3%) and angina pectoris (1%).
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Grade 3 and 4 increased ALT or AST was seen in 9% of patients. Grade ≥2 increased ALT or AST was reported in 64 (18%) patients, of whom 20 (31%) received ≥40 mg daily oral prednisone equivalent. Recurrence of Grade ≥2 increased ALT or AST was observed on rechallenge in 10 patients receiving both KEYTRUDA and lenvatinib (n=38) and was not observed on rechallenge with KEYTRUDA alone (n=3).

Endometrial Carcinoma
The safety of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-775, a multicenter, open-label, randomized (1:1), active-controlled trial in 827 patients with advanced endometrial carcinoma previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings [see Clinical Studies (14.15)]. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients received KEYTRUDA 200 mg intravenously every 3 weeks with lenvatinib 20 mg orally once daily (n=406), or treatment of investigator's choice (n=388), consisting of 60 mg/m2 doxorubicin every 3 weeks or 80 mg/m2 paclitaxel given weekly, 3 weeks on/1 week off.
The median duration of study treatment was 7.6 months (range 1 day to 26.8 months). The median duration of exposure to KEYTRUDA was 6.9 months (range: 1 day to 25.8 months). KEYTRUDA was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months.
Fatal adverse reactions occurred in 5.7% of patients treated with KEYTRUDA and lenvatinib, including pneumonia, acute kidney injury, acute myocardial infarction, cerebrovascular accident, colitis, decreased appetite, intestinal perforation, lower gastrointestinal hemorrhage, malignant gastrointestinal obstruction, multiple organ dysfunction syndrome, myelodysplastic syndrome, pulmonary embolism, right ventricular dysfunction, urosepsis, and vaginal hemorrhage.
Serious adverse reactions occurred in 53% of patients receiving KEYTRUDA and lenvatinib. Serious adverse reactions with frequency ≥3% were hypertension (4.2%) and urinary tract infections (3.2%).
Discontinuation of KEYTRUDA, lenvatinib or both due to an adverse reaction (Grades 1-4) occurred in 30% of patients; 15% KEYTRUDA, and 11% both drugs. The most common adverse reactions leading to discontinuation of KEYTRUDA were diarrhea, increased ALT, and intestinal obstruction (each 1.0%). Refer to the lenvatinib prescribing information for lenvatinib discontinuation information.
Dose interruptions of KEYTRUDA, lenvatinib, or both due to an adverse reaction occurred in 69% of patients; KEYTRUDA was interrupted in 50%, and both drugs were interrupted in 31% of patients. The most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were diarrhea (8%),

increased ALT (3.9%), hypertension (3.4%), increased AST (3.2%), decreased appetite (2.2%), fatigue (2.2%), urinary tract infection (2.2%), proteinuria (2.0%), and asthenia (2.0%). Refer to the lenvatinib prescribing information for lenvatinib interruption information.
Tables 32 and 33 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in combination with lenvatinib in KEYNOTE-775.

8.5 Geriatric Use

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Of 406 adult patients with endometrial carcinoma who were treated with KEYTRUDA in combination with lenvatinib in KEYNOTE-775, 201 (50%) were 65 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

14 CLINICAL STUDIES

עודכן מידע לגבי ההתוויות:

Renal Cell Carcinoma - First-line treatment with axitinib
Renal Cell Carcinoma - First-line treatment with lenvatinib
Endometrial Carcinoma - in combination with lenvatinib

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

1. למה מיועדת קיטרודה?
קיטרודה הינה תרופת מרשם המשמשת לטיפול ב:
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- סרטן כליה הנקרא קרצינומה של תאי הכליה (RCC).
  - ניתן להשתמש ב**קיטרודה** בשילוב עם התרופה אקסיטיניב כטיפול הראשון שלך כאשר סרטן הכליה שלך התפשט או שאין אפשרות להסירו על ידי ניתוח (RCC מתקדם).
  - ניתן להשתמש ב**קיטרודה** בשילוב עם התרופה לנווטיניב כטיפול הראשון שלך כאשר סרטן הכליה שלך התפשט או שאין אפשרות להסירו על ידי ניתוח (RCC מתקדם).
- סרטן רחם מסוג קרצינומה של רירית הרחם.
  - ניתן להשתמש ב**קיטרודה** בשילוב עם התרופה לנווטיניב:
    - כאשר קיבלת טיפול כנגד הסרטן והוא אינו פועל יותר, **ו**
    - הסרטן שלך לא ניתן לריפוי על ידי ניתוח או קרינה (סרטן מתקדם של רירית הרחם).

4. תופעות לוואי
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תופעות לוואי שכיחות מאד של קיטרודה כאשר ניתנת בשילוב עם לנווטיניב כוללות:
(דווחו ביותר מ- 20% מהמטופלים)
כללי: הרגשת עייפות, ירידה במשקל
מערכת העיכול: שלשול, פצעים בפה, בחילה, כאב באזור הקיבה (בטן), הקאה, עצירות
שריר-שלד ורקמת חיבור: כאב במפרק ובשריר
המערכת ההורמונלית: רמות נמוכות של הורמון בלוטת התריס
כלי הדם: לחץ דם גבוה, דימום
מטבוליזם ותזונה: ירידה בתאבון
עור ורקמה תת עורית: פריחה, שלפוחיות או פריחה בכפות הידיים שלך וכפות הרגליים שלך
מערכת הנשימה, בית החזה, חלל הבינה (מדיאסטינום): צרידות
מערכת השתן והכליות: חלבון בשתן שלך, בעיות בכליה
זיהומים: זיהום בדרכי השתן
כבד ומרה: בעיות בכבד
מערכת העצבים: כאב ראש

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) ≥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 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.

Classical Hodgkin Lymphoma
KEYTRUDA is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL).
KEYTRUDA is indicated for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more 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.

Non-Muscle Invasive Bladder Cancer (NMIBC)
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).
KEYTRUDA, in combination with lenvatinib, is indicated for the first-line treatment of adult patients with advanced RCC.

Tumor Mutational Burden-High (TMB-H) Cancer
KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by a validated test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with TMB-H central nervous system cancers have not been established.

Esophageal Cancer
•KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (Siewert type I) carcinoma that is not amenable to surgical resection or definitive chemoradiation in combination with platinum- and fluoropyrimidine-based chemotherapy.

•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.

Cutaneous Squamous Cell Carcinoma
KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC that is not curable by surgery or radiation.

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC)
KEYTRUDA is indicated for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

Triple negative breast cancer (TNBC)
KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic triple negative breast cancer (TNBC) whose tumors express PD-L1 (CPS ≥10) as determined by a validated test.

Endometrial carcinoma
Keytruda, in combination with lenvatinib, is indicated for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum containing therapy and who are not candidates for curative surgery or radiation.

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

העלון לרופא ולצרכן נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפס 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:
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Keytruda_100mg_4ml-PIL-HEB-04_2022