

אוגוסט 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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### 1.18 Triple Negative Breast Cancer

KEYTRUDA is indicated for the treatment of patients with high-risk early-stage triple negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

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  $\geq 10$ ) as determined by a validated test.

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## 2 DOSAGE AND ADMINISTRATION

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### 2.19 Recommended Dosage for TNBC

The recommended dose of KEYTRUDA in adult patients with high-risk early-stage TNBC for neoadjuvant treatment is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks in combination with chemotherapy for 24 weeks (8 doses of 200mg every 3 weeks) or until disease progression or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as a single agent for up to 27 weeks (9 doses of 200 mg every 3 weeks) or until disease recurrence or unacceptable toxicity.

Administer KEYTRUDA prior to chemotherapy when given on the same day. Refer to the Prescribing Information for the chemotherapy agents administered in combination with KEYTRUDA, for recommended dosing information, as appropriate. Patients who experience disease progression or unacceptable toxicity related to KEYTRUDA with neoadjuvant treatment in combination with chemotherapy should not receive adjuvant single agent KEYTRUDA.

The recommended dose of KEYTRUDA in patients with locally recurrent unresectable or metastatic TNBC is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks in combination to chemotherapy until disease progression, unacceptable toxicity, or up to 24 months.

Administer KEYTRUDA prior to chemotherapy when given on the same day. Refer to the Prescribing Information for the chemotherapy agents administered in combination with KEYTRUDA, for recommended dosing information, as appropriate.

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## 5 WARNINGS AND PRECAUTIONS

### 5.1 Severe and Fatal Immune-Mediated Adverse Reactions

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Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. For patients with TNBC treated with KEYTRUDA in the neoadjuvant setting, monitor blood cortisol at baseline, prior to surgery, and as clinically indicated. In cases of suspected immune-mediated adverse reactions, initiate

appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

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## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

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#### TNBC

##### Neoadjuvant and Adjuvant Treatment of High-Risk Early-Stage TNBC

The safety of KEYTRUDA in combination with neoadjuvant chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide) followed by surgery and continued adjuvant treatment with KEYTRUDA as a single agent was investigated in KEYNOTE-522, a randomized (2:1), multicenter, double-blind, placebo-controlled trial in patients with newly diagnosed, previously untreated, high-risk early-stage TNBC.

A total of 778 patients on the KEYTRUDA arm received at least 1 dose of KEYTRUDA in combination with neoadjuvant chemotherapy followed by KEYTRUDA as adjuvant treatment after surgery, compared to 389 patients who received at least 1 dose of placebo in combination with neoadjuvant chemotherapy followed by placebo as adjuvant treatment after surgery [see Clinical Studies (14.18)].

The median duration of exposure to KEYTRUDA 200 mg every 3 weeks was 13.3 months (range: 1 day to 21.9 months).

Fatal adverse reactions occurred in 0.9% of patients receiving KEYTRUDA, including 1 each of adrenal crisis, autoimmune encephalitis, hepatitis, pneumonia, pneumonitis, pulmonary embolism, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction.

Serious adverse reactions occurred in 44% of patients receiving KEYTRUDA. Serious adverse reactions in  $\geq 2\%$  of patients who received KEYTRUDA included febrile neutropenia (15%), pyrexia (3.7%), anemia (2.6%), and neutropenia (2.2%).

KEYTRUDA was discontinued for adverse reactions in 20% of patients. The most common adverse reactions ( $\geq 1\%$ ) resulting in permanent discontinuation of KEYTRUDA were increased ALT (2.7%), increased AST (1.5%), and rash (1%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 57% of patients. The most common adverse reactions leading to interruption of KEYTRUDA ( $\geq 2\%$ ) were neutropenia (26%), thrombocytopenia (6%), increased ALT (6%), increased AST (3.7%), anemia (3.5%), rash (3.2%), febrile neutropenia (2.8%), leukopenia (2.8%), upper respiratory tract infection (2.6%), pyrexia (2.2%), and fatigue (2.1%).

Tables 36 and 37 summarize the adverse reactions and laboratory abnormalities, respectively, in patients treated with KEYTRUDA in KEYNOTE-522.

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## 14 CLINICAL STUDIES

עודכן מידע לגבי ההתוויות:

14.1 Melanoma - Adjuvant Treatment of Stage III Resected Melanoma

14.18 Triple Negative Breast Cancer - Neoadjuvant and Adjuvant Treatment of High-Risk Early-Stage TNBC

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

### 1. למה מיועדת קיטרודה?

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- סרטן שד מסוג טריפל-נגטיב (Triple-Negative Breast Cancer, TNBC).
- ניתן להשתמש בקיטרודה בשילוב עם תרופות כימותרפיות כטיפול לפני ניתוח ואז להמשיך בקיטרודה לבדה כטיפול אחרי ניתוח כאשר:
  - יש לך סרטן שד בשלב מוקדם. I
  - הינך בסיכון גבוה לחזרה של סרטן השד שלך.

- ניתן להשתמש בקיטרודה בשילוב עם תרופות כימותרפיות כאשר סרטן השד שלך:
- חזר ולא ניתן להסירו על ידי ניתוח או התפשט, ו
- הינו חיובי ל-"PD-L1".

#### 4. תופעות לוואי

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תופעות לוואי שכיחות מאוד של קיטרודה כאשר ניתנת בשילוב עם תרופות כימותרפיות מסוימות כוללות:

(דווחו ביותר מ-10% מהמטופלים)  
מערכת העיכול: בחילה, עצירות, שלשול, הקאה, קשיים בבליעה, כאב באזור הקיבה (בטן)

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שריר-שלד ורקמת חיבור: כאב בשרירים, כאב בצוואר, כאב במפרק ובשריר

#### התוויות 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)  $\geq 1$ ] 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  $\geq 10$ )] 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)  $\geq 1$ ] 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  $\geq 1$ ) as determined by a validated test.

KEYTRUDA, in combination with chemotherapy, with or without bevacizumab, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS  $\geq 1$ ) 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.

KEYTRUDA is indicated for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

#### 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) [ $\geq 10$  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  $\geq 10$ ) 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  $\geq 10$ ) as determined by a validated test.

KEYTRUDA is indicated for the treatment of patients with high risk early stage triple negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

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:

Keytruda\_100mg\_4ml-SPC-08\_2022

Keytruda\_100mg\_4ml-PIL-HEB-08\_2022