ספטמבר 2025

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 והעלון לצרכן של התכשיר Keytruda 100mg/4ml להכללת התוויה חדשה והעדכונים עפ"י המפורט מטה.

(טקסט שהוסף לעלון לרופא ולצרכן מודגש בקו תחתון, טקסט שנמחק מהעלון לרופא ולצרכן מסומן בקו חוצה)

עדכונים שבוצעו בעלון לרופא:

1 THERAPEUTIC INDICATIONS
[…]
1.3 Malignant Pleural Mesothelioma
KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma.
[…]

2 Dosage and administration
2.1 Patient Selection
[…]
Patient Selection for Combination Therapy
For use of KEYTRUDA in combination with chemotherapy ~~and trastuzumab~~, select patients based on the presence of positive PD-L1 expression (CPS ≥1) in locally advanced unresectable or metastatic ~~HER-2 positive~~ gastric or gastroesophageal junction (GEJ) adenocarcinoma *[see Clinical Studies (14.10)].*

[…]
2.4 Recommended Dosage for MPM
The recommended dose of KEYTRUDA in patients with MPM is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity or up to 24 months.

When administering KEYTRUDA in combination with chemotherapy, 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.
[…]

6 ADVERSE REACTIONS
[…]
6.1 Clinical Trials Experience
[…]
Malignant Pleural Mesothelioma (MPM)

First-line treatment of unresectable advanced or metastatic MPM with pemetrexed and platinum chemotherapy

The safety of KEYTRUDA in combination with pemetrexed and platinum chemotherapy (either carboplatin or cisplatin) was investigated in KEYNOTE-483, a multicenter, open-label, randomized (1:1), active-controlled trial in patients with previously untreated, unresectable advanced or metastatic MPM *[see Clinical Studies (14.3)]*. A total of 473 patients received KEYTRUDA 200 mg, pemetrexed, and platinum every 3 weeks for up to 6 cycles followed by KEYTRUDA (n=241), or pemetrexed and platinum chemotherapy every 3 weeks for up to 6 cycles (n=232). Patients with autoimmune disease that required systemic therapy within 3 years of treatment or a medical condition that required immunosuppression were ineligible.

The median duration of exposure to KEYTRUDA 200 mg every 3 weeks was 6.9 months (range: 1 day to 25.2 months). Sixty-one percent of patients in the KEYTRUDA arm were exposed to KEYTRUDA for ≥6 months.

Adverse reactions occurring in patients with MPM were generally similar to those in other patients receiving KEYTRUDA in combination with pemetrexed and platinum chemotherapy.

[…]

Cervical Cancer

FIGO 2014 Stage III-IVA Cervical Cancer with Chemoradiotherapy

The safety of KEYTRUDA in combination with CRT (cisplatin plus external beam radiation therapy [EBRT] followed by brachytherapy [BT]) was investigated in KEYNOTE-A18, a placebo-controlled, randomized (1:1), multicenter, double-blind trial including ~~594~~597 patients with FIGO 2014 Stage III-IVA cervical cancer *[see Clinical Studies (14.12)]*. Two hundred ninety ~~two~~ four patients received KEYTRUDA in combination with chemoradiotherapy and ~~302~~303 patients received placebo in combination with chemoradiotherapy.

The median duration of exposure to KEYTRUDA was ~~12.1~~20 months (range: 1 day to ~~27~~32 months).

Fatal adverse reactions occurred in 1.4% of patients receiving KEYTRUDA in combination with chemoradiotherapy, including 1 case each (0.3%) of large intestinal perforation, urosepsis, sepsis, and vaginal hemorrhage.

Serious adverse reactions occurred in ~~30~~34% of patients receiving KEYTRUDA in combination with chemoradiotherapy. Serious adverse reactions occurring in ≥1% of patients included urinary tract infection (~~2.7~~3.1%), urosepsis (1.4%), and sepsis (1%).

KEYTRUDA was discontinued for adverse reactions in ~~7~~9% of patients. The most common adverse reaction (≥1%) resulting in permanent discontinuation was diarrhea (1%).

Adverse reactions leading to interruption of KEYTRUDA occurred in ~~43~~47% of patients; the most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were anemia (~~8~~7%), COVID-19 (~~6~~7%), SARS-CoV-2 test positive (~~3.14~~4.8%), diarrhea (4.1%), increased ALT (4.1%), increased AST (3.4%) decreased neutrophil count (~~2.7~~3.1%), and ~~diarrhea (2.7%),~~ urinary tract infection (2.7%), ~~and increased ALT (2.4%)~~.

Tables 1 and 2 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-A18.

Table 1: Adverse Reactions Occurring in ≥10% of Patients with FIGO 2014 Stage III-IVA Cervical Cancer Receiving KEYTRUDA in KEYNOTE-A18

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and 400 mg every 6 weeks with chemoradiotherapy n=294~~2~~		Placebo with chemoradiotherapy n=303~~2~~	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
Gastrointestinal				
Nausea	56	0	62~~61~~	2.3
Diarrhea	51~~50~~	4.4~~3.8~~	50	4.3
Vomiting	34~~33~~	1.0	35~~34~~	1.7
Constipation	20~~18~~	0	19~~18~~	0.7
Abdominal pain	13~~12~~	1.0~~0.7~~	14~~12~~	1.7
Infections				
Urinary tract infection†	35~~32~~	4.8~~4.1~~	34~~31~~	~~5~~4.6
COVID-19	10	0	7	1.0
General				
Fatigue‡	28~~26~~	1.0	28~~27~~	1.3
Pyrexia	14~~12~~	0.7~~0.3~~	15~~13~~	0
Endocrine				
Hypothyroidism§	23~~20~~	0.7	~~8~~5	0
Hyperthyroidism	13~~11~~	0.3	3.3~~2.6~~	0
Investigations				
Weight loss	19	2.4	19	1.0
Metabolism and Nutrition				
Decreased appetite	18~~17~~	0.7	17	0.3

~~**Investigations**~~				
~~Weight loss~~	~~17~~	~~1.4~~	~~18~~	~~1~~
Renal and Urinary				
Dysuria	1211	0.3	12	0
Skin and Subcutaneous Tissue Disorders				
Rash¶	1211	1.00.7	87	0.3
Musculoskeletal and Connective Tissues Disorders				
Back pain	11	0.7	11	0.7
Reproductive System				
Pelvic pain	1110	1.0	1413	1.71.3

* Graded per NCI CTCAE v5.0
† Includes urinary tract infection, urinary tract infection pseudomonal, pyelonephritis acute, cystitis, Escherichia urinary tract infection
‡ Includes fatigue, asthenia
§ Includes hypothyroidism, autoimmune hypothyroidism
¶ Includes erythema multiforme, dermatitis, drug eruption, eczema, rash, skin exfoliation, dermatitis bullous, rash maculo-papular, lichen planus, dyshidrotic eczema, dermatitis acneiform

Table 2: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients with FIGO 2014 Stage III-IVA Cervical Cancer Receiving KEYTRUDA in KEYNOTE-A18

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and 400 mg every 6 weeks with chemoradiotherapy		Placebo with chemoradiotherapy	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Hematology				
Lymphopenia	99	96	99	92
Leukopenia	96	4846	94	49
Anemia	8788	3331	8281	2725
Neutropenia	7675	3332	7674	33
Thrombocytopenia	6465	98	6261	76
Chemistry				
Hypomagnesemia	6159	4.2	63	3.73.4
Hyponatremia	5654	4.83.8	5047	4.7
Increased AST	5045	1.7	4439	2.31.7
Increased ALT	4944	3.12.1	4644	1
Hypocalcemia	4543	54.8	4340	54.3
Hypokalemia	4442	1514	4138	1110
Increased creatinine	4441	76	4643	6
Hypoalbuminemia	3837	2.40.7	3735	2.31.7
Increased alkaline phosphatase	3834	0.3	3533	0.3
Hyperkalemia	21	2.0	16	1

* Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter: KEYTRUDA + chemoradiotherapy (range: 2886 to 2931 patients) and placebo + chemoradiotherapy (range: 2998 to 3010 patients)
† Graded per NCI CTCAE v5.0

[…]
8.5 Geriatric Use
[…]
Of 2942 adult patients with FIGO 2014 Stage III-IVA cervical cancer who were treated with KEYTRUDA in combination with CRT in KEYNOTE-A18, 42 (14%) were 65 years and over. No overall differences in safety ~~or efficacy were~~was observed between ~~elderly~~ patients ≥65 years of age and younger patients.

בוצעו עדכונים ונוסף מידע בסעיפים המפורטים מטה:

14 CLINICAL STUDIES
14.2 Non-Small Cell Lung Cancer
14.3 Malignant Pleural Mesothelioma
14.12 Cervical Cancer

עדכונים שבוצעו בעלון לצרכן:
[....]
1. למה מיועדת קיטרודה?
קיטרודה הינה תרופת מרשם המשמשת לטיפול ב:
[....]
- סוג של סרטן שנקרא מזותליומה פלאורלית ממאירה (MPM)במבוגרים המשפיע על מעטפת הריאות ודופן בית החזה.
  - ניתן להשתמש ב**קיטרודה** בשילוב עם התרופה הכימותרפית פמטרקסד וכימותרפיה מבוססת פלטינום כטיפול קו ראשון כשהסרטן שלך:
    - הינו מסוג שנקרא "לא אפיתליאלי", **ו**
    - לא ניתן להסרה בניתוח.

[....]
4.תופעות לוואי
[....]
תופעות הלוואי הבאות דווחו עם קיטרודה כאשר ניתנת בשילוב עם תרופות כימותרפיות או עם תרופות כימותרפיות וטיפול קרינתי:
[....]
תופעות לוואי שכיחות מאוד (דווחו ב- 10% עד פחות מ- 20% מהמטופלים)
- רמות גבוהות של הורמון בלוטת התריס
- קשיים בבליעה
- זיהום בריאות
- גרד
- כאב או צריבה בזמן הטלת שתן
- כאב באזור האגן
- כאב צוואר
- סחרחורת
- קוביד-19
- כאב גב

בעלון לרופא בוצעו עידכונים נוספים שאינם נכללים בהודעה זו.
למידע מלא ולהוראות מתן מפורטות, יש לעיין בעלון לרופא המאושר על ידי משרד הבריאות.
העלון לרופא 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.
דיווח על תופעות לוואי לתכשירים רשומים הינו חשוב ומאפשר המשך מעקב אחר מאזן התועלת/סיכון של התכשיר. ניתן לדווח על תופעות לוואי למשרד הבריאות באמצעות לחיצה על הקישור "דיווח על תופעות לוואי עקב טיפול תרופתי" שנמצא בדף הבית של אתר משרד הבריאות (www.health.gov.il) המפנה לטופס המקוון לדיווח על תופעות לוואי, או ע"י כניסה לקישור: https://sideeffects.health.gov.il . כמו כן ניתן לדווח על תופעות לוואי לחברת MSD ישראל באמצעות פנייה טלפונית ל--09-9533333.

בברכה,
דורית מאורי
רוקחת ממונה
MSD ישראל

References:
Keytruda_100mg_4ml-SPC-09_2025_clean
Keytruda_100mg_4ml-PIL-HEB-09_2025_clean

ההתוויות המאושרות לתכשיר:

Melanoma

- KEYTRUDA is indicated for the treatment of adult and pediatric (12 years and older) patients with unresectable or metastatic melanoma.
- KEYTRUDA is indicated for the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma 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.
- KEYTRUDA, as a single agent, is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC.
- KEYTRUDA, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable NSCLC at high risk of recurrence in adults (for selection criteria, see section 14 CLINICAL STUDIES).

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 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 Cancer

- KEYTRUDA, as a single agent, 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 PDL1 (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, as a single agent, 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, as a single agent, 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.
- KEYTRUDA, in combination with enfortumab vedotin, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer.

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, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction (GEJ) adenocarcinoma in adults whose tumors express PD-L1 with a CPS ≥1 as determined by a validated test.
- KEYTRUDA, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 with a CPS ≥1 as determined by a validated test.

Cervical Cancer

- KEYTRUDA, in combination with chemoradiotherapy (CRT), is indicated for the treatment of patients with FIGO 2014 Stage III-IVA cervical cancer.
- 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 ≥1) as determined by a validated test.
- KEYTRUDA, as a single agent, 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.

Biliary Tract Cancer

KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the treatment of patients with locally advanced unresectable or metastatic biliary tract cancer (BTC).

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 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.
- 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.

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).

Tumor Mutational Burden-High 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.

Triple Negative Breast Cancer
- 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.
- 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 carboplatin and paclitaxel, followed by KEYTRUDA as a single agent, for the treatment of adult patients with primary advanced or recurrent pMMR endometrial carcinoma at least 12 months from prior adjuvant chemotherapy, and dMMR endometrial carcinoma regardless of prior adjuvant treatment.
- 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.

Malignant Pleural Mesothelioma
KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma.