הודעה על החמרה (מידע בטיחות) בעלון לרופא

תאריך: 25 באוקטובר 2017

שם תכשיר באנגלית: Keytruda 50mg; Keytruda 100mg/4ml

מספר רישום: 153.43.34324.00 154.38.34448.00

שם בעל הרישום: חברת מרק שארפ ודוהם (ישראל-1996) בע"מ

ההחמרות המבוקשות

טקסט חדש	טקסט נוכחי	פרק בעלון
Withhold KEYTRUDA for any of the following: Grade 4 hematological toxicity in cHL patients. Resume KEYTRUDA in patients whose adverse reactions recover to Grade 0-1.		**Dose Modifications**
5.6 Immune-Mediated Skin Adverse Reactions Immune-mediated rashes, including SJS, TEN (some cases with fatal outcome), exfoliative dermatitis, and bullous pemphigoid, can occur. Monitor patients for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA. *[See Dosage and Administration (2.7).]*	~~**5.6 Severe Skin Reactions**~~ ~~Immune-mediated severe skin reactions have been reported in patients treated with KEYTRUDA. Monitor patients for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids *[see Dosage and Administration (2.5)].*~~ ~~Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients treated with KEYTRUDA. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA *[see Dosage and Administration (2.5)].*~~	**Warning and precautions- Immune- Mediated Skin Adverse Reactions**
5.7 Other Immune-Mediated Adverse Reactions KEYTRUDA can cause other clinically important immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system… …In addition, myelitis and myocarditis were reported in other clinical trials, including cHL, and post-marketing use.		**Warning and precautions- Other Immune- Mediated Adverse Reactions**
5.8 Infusion-Related Reactions KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA. Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue KEYTRUDA *[see Dosage and Administration (2.7**)**].*		**Warning and precautions- Infusion-related reactions**

5.9 Complications of Allogeneic HSCT after 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 immunemediated adverse reactions, and intervene promptly.		**Warning and precautions-Complications of Allogeneic HSCT after KEYTRUDA**

cHL Among the 210 patients with cHL enrolled in Study KEYNOTE-087 *[see Clinical Studies (14.4)]*, the median duration of exposure to KEYTRUDA was 8.4 months (range: 1 day to 15.2 months). KEYTRUDA was discontinued due to adverse reactions in 5% of patients, and treatment was interrupted due to adverse reactions in 26%. Fifteen percent (15%) of patients had an adverse reaction requiring systemic corticosteroid therapy. Serious adverse reactions occurred in 16% of patients. The most frequent serious adverse reactions (≥1%) included pneumonia, pneumonitis, pyrexia, dyspnea, graft versus host disease and herpes zoster. Two patients died from causes other than disease progression; one from GVHD after subsequent allogeneic HSCT and one from septic shock. Table 7 summarizes the adverse reactions that occurred in at least 10% of patients treated with KEYTRUDA. Other clinically important adverse reactions that occurred in less than 10% of patients on KEYNOTE 087 included infusion reactions (9%), hyperthyroidism (3%), pneumonitis (3%), uveitis and myositis (1% each), myelitis and myocarditis (0.5% each). Hyperbilirubinemia occurred in less than 15% of patients on KEYNOTE-087 (10% all Grades, 2.4% Grade 3-4). Table 7: Adverse Reactions in ≥10% of Patients with cHL in KEYNOTE-087- *included in attachement* Table 8: Selected Laboratory abnormalities Worsened from Baseline Occurring in ≥15% of cHL Patients Receiving KEYTRUDA in KEYNOTE-087- *included in attachement*		**Adverse reactions- Clinical Trials Experience**

Urothelial Carcinoma Previously Treated Urothelial Carcinoma The safety of KEYTRUDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma with disease progression following platinum-containing chemotherapy was investigated in Study KEYNOTE-045. KEYNOTE-045 was a multicenter, open-label, randomized (1:1), active-controlled trial in which 266 patients received KEYTRUDA 200 mg every 3 weeks or investigator's choice of chemotherapy (n=255), consisting of paclitaxel (n=84), docetaxel (n=84) or vinflunine (n=87) *[see Clinical Studies (14.4)]*. Patients with autoimmune disease or a medical condition that required systemic corticosteroids or other immunosuppressive medications were ineligible. The median duration of exposure was 3.5 months (range: 1 day to 20 months) in patients who received KEYTRUDA and 1.5 months (range: 1 day to 14 months) in patients who received chemotherapy. KEYTRUDA was discontinued due to adverse reactions in 8% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.9%). Adverse reactions leading to interruption of KEYTRUDA occurred in 20% of patients; the most common (≥1%) were urinary tract infection (1.5%), diarrhea (1.5%), and colitis (1.1%). The most common adverse reactions (occurring in at least 20% of patients who received KEYTRUDA) were fatigue, musculoskeletal pain, pruritus, decreased appetite, nausea and rash. Serious adverse reactions occurred in 39% of KEYTRUDA-treated patients. The most frequent serious adverse reactions (≥2%) in KEYTRUDA-treated patients were urinary tract infection, pneumonia, anemia, and pneumonitis. Table 9 summarizes the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA. Table 13 summarizes the incidence of laboratory abnormalities that occurred in at least 20% of patients receiving KEYTRUDA. Table 9: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-045- *included in attachement* Table 10: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Urothelial Carcinoma Patients Receiving KEYTRUDA in KEYNOTE-045- *included in attachement*		**Adverse reactions- Clinical Trials Experience**

הודעה על החמרה (מידע בטיחות) בעלון לצרכן

תאריך: 25 באוקטובר 2017

שם תכשיר באנגלית: Keytruda 50mg; Keytruda 100mg/4ml

מספר רישום: 153.43.34324.00 ,154.38.34448.00

שם בעל הרישום: חברת מרק שארפ ודוהם (ישראל-1996) בע"מ

ההחמרות המבוקשות		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
תופעות לוואי	**סימנים ותסמינים של בעיות בעור.** סימנים של בעיות בעור יכולים לכלול: פריחה; גרוד; שלפוחיות, קילוף או פצעים בעור; כיבים בפה או בדופן האף, בגרון או באזור אברי המין.	**בעיות בעור.** סימנים של בעיות בעור יכולים לכלול: פריחה; גרוד; שלפוחיות, קילוף או פצעים בעור; פצעים או כיבים כואבים בפה שלך או באף, בגרון או באזור אברי המין שלך.

תופעות לוואי		**דחייה של איברים מושתלים**. אנשים שעברו השתלת איברים עלולים להיות בעלי סיכון מוגבר לדחיית האיבר המושתל במידה והם מטופלים ב**קיטרודה**. על הרופא שלך לומר לך על אילו סימנים ותסמינים עליך לדווח, והוא יבצע מעקב, בהתאם לסוג השתלת האיברים שהיתה לך.
תופעות לוואי		**סיבוכים של השתלת תאי גזע מתורם (אלוגנאית) לאחר טיפול בקיטרודה**. סיבוכים אלו עלולים להיות חמורים ולהוביל למוות. אם עברת השתלת תאי גזע אלוגנאית, הרופא שלך יבצע מעקב לזיהוי סימנים המעידים על סיבוכים
תופעות לוואי		תופעות לוואי שכיחות של **קיטרודה** כוללות: הרגשת עייפות, גרוד, שלשול, ירידה בתיאבון, פריחה, חום, שיעול, קוצר נשימה, כאב בשרירים, עצמות או מפרקים, עצירות, ובחילה. בילדים, הרגשת עייפות, הקאות וכאב באזור הבטן, עלייה ברמות אנזימי הכבד וירידה ברמות המלח בדם (נתרן) הינם שכיחים יותר מאשר במבוגרים.

Table 7: Adverse Reactions in ≥10% of Patients with cHL in KEYNOTE-087

	KEYTRUDA 200 mg every 3 weeks N=210	
Adverse Reaction	All Grades* (%)	Grade 3 (%)
General Disorders and Administration Site Conditions		
Fatigue[†]	26	1.0
Pyrexia	24	1.0
Respiratory, Thoracic and Mediastinal Disorders		
Cough[‡]	24	0.5
Dyspnea[§]	11	1.0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[¶]	21	1.0
Arthralgia	10	0.5
Gastrointestinal Disorders		
Diarrhea[#]	20	1.4
Vomiting	15	0
Nausea	13	0
Skin and Subcutaneous Tissue Disorders		
Rash[Þ]	20	0.5
Pruritus	11	0
Endocrine Disorders		
Hypothyroidism	14	0.5
Infections and Infestations		
Upper respiratory tract infection	13	0
Nervous System Disorders		
Headache	11	0.5
Peripheral neuropathy[β]	10	0

* Graded per NCI CTCAE v4.0
† Includes fatigue, asthenia
‡ Includes cough, productive cough
§ Includes dyspnea, dyspnea exertional, wheezing
¶ Includes back pain, myalgia, bone pain, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain
# Includes diarrhea, gastroenteritis, colitis, enterocolitis
Þ Includes rash, rash maculo-papular, drug eruption, eczema, eczema asteatotic, dermatitis, dermatitis acneiform, dermatitis contact, rash erythematous, rash macular, rash papular, rash pruritic, seborrhoeic dermatitis, dermatitis psoriasiform
β Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paresthesia, dysesthesia, polyneuropathy

Table 8: Selected Laboratory Abnormalities Worsened from Baseline Occurring in ≥15% of cHL Patients Receiving KEYTRUDA in KEYNOTE-087

	KEYTRUDA 200 mg every 3 weeks	
Laboratory Test*	All Grades† (%)	Grade 3-4 (%)
Chemistry		
Hypertransaminasemia‡	34%	2%
Alkaline phosphatase increased	17%	0%
Creatinine increased	15%	0.5%
Hematology		
Anemia	30%	6%
Thrombocytopenia	27%	4%
Neutropenia	24%	7%

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 208 to 209 patients)
† Graded per NCI CTCAE v4.0
‡ Includes elevation of AST or ALT

Table 9: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE 045

	KEYTRUDA 200 mg every 3 weeks n=266		Chemotherapy* n=255	
Adverse Reaction	**All Grades† (%)**	**Grade 3-4 (%)**	**All Grades† (%)**	**Grade 3-4 (%)**
Gastrointestinal Disorders				
Nausea	21	1.1	29	1.6
Constipation	19	1.1	32	3.1
Diarrhea‡	18	2.3	19	1.6
Vomiting	15	0.4	13	0.4
Abdominal pain	13	1.1	13	2.7
General Disorders and Administration Site Conditions				
Fatigue§	38	4.5	56	11
Pyrexia	14	0.8	13	1.2
Infections and Infestations				
Urinary tract infection	15	4.9	14	4.3
Metabolism and Nutrition Disorders				
Decreased appetite	21	3.8	21	1.2
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain¶	32	3.0	27	2.0
Renal and Urinary Disorders				
Hematuria#	12	2.3	8	1.6
Respiratory, Thoracic and Mediastinal Disorders				
Cough Þ	15	0.4	9	0
Dyspnea ß	14	1.9	12	1.2
Skin and Subcutaneous Tissue Disorders				
Pruritus	23	0	6	0.4
Rash à	20	0.4	13	0.4

* Chemotherapy: paclitaxel, docetaxel, or vinflunine
† Graded per NCI CTCAE v4.0
‡ Includes diarrhea, gastroenteritis, colitis, enterocolitis
§ Includes asthenia, fatigue, malaise lethargy
¶ Includes back pain, myalgia, bone pain, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain
# Includes blood urine present, hematuria, chromaturia
Þ Includes cough, productive cough
ß Includes dyspnea, dyspnea exertional, wheezing
à Includes rash maculo-papular, rash genital rash, rash erythematous, rash papular, rash pruritic, rash pustular, erythema, drug eruption, eczema, eczema asteatotic, dermatitis contact, dermatitis acneiform, dermatitis, seborrhoeic keratosis, lichenoid keratosis

Table 10: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Urothelial Carcinoma Patients Receiving KEYTRUDA in KEYNOTE 045

	KEYTRUDA 200 mg every 3 weeks		Chemotherapy	
Laboratory Test*	**All Grades† %**	**Grades 3-4 %**	**All Grades† %**	**Grades 3-4 %**
Chemistry				
Glucose increased	52	8	60	7
Hemoglobin decreased	52	13	68	18
Lymphocytes decreased	45	15	53	25
Albumin decreased	43	1.7	50	3.8
Sodium decreased	37	9	47	13
Alkaline phosphatase increased	37	7	33	4.9
Creatinine increased	35	4.4	28	2.9
Phosphate decreased	29	8	34	14
Aspartate aminotransferase increased	28	4.1	20	2.5
Potassium increased	28	0.8	27	6
Calcium decreased	26	1.6	34	2.1

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 240 to 248 patients) and chemotherapy (range: 238 to 244 patients); phosphate decreased: KEYTRUDA n=232 and chemotherapy n=222.

† Graded per NCI CTCAE v4.0