Bristol Myers Squibb™

אוגוסט 2022

YERVOY 5mg/ml
Concentrate for solution for infusion
יירבוי 5 מ"ג/מ"ל
תמיסה מרוכזת להכנת תמיסה לעירוי

רופא/ה ,רוקח/ת יקר/ה,

חברת בריסטול-מאיירס סקוויב (ישראל) מבקשת להודיע על עדכון בעלון לרופא ובעלון לצרכן של התכשיר שבנדון.

התוויות התכשיר כפי שמאושרות ע"י משרד הבריאות:

1.1 Unresectable or Metastatic Melanoma

YERVOY (ipilimumab) is indicated for the treatment of advanced (unresectable or metastatic) melanoma.
YERVOY (ipilimumab), in combination with nivolumab, is indicated for the treatment of patients with advanced (unresectable or metastatic) melanoma.

1.2 Advanced Renal Cell Carcinoma

YERVOY, in combination with nivolumab, is indicated for the first-line treatment of patients with intermediate or poor risk, advanced renal cell carcinoma (RCC)

1.3 Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer

YERVOY, in combination with nivolumab, is indicated for the treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

1.4 Metastatic Non-Small Cell Lung Cancer

YERVOY, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC) with no EGFR or ALK genomic tumor aberrations.

1.5 Hepatocellular Carcinoma

Yervoy, in combination with nivolumab, is indicated for the treatment of patients with hepatocellular carcinoma (HCC) Child-Pugh A who have been previously treated with sorafenib.

1.6 Malignant Pleural Mesothelioma

YERVOY, in combination with nivolumab, is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

המרכיב הפעיל: Ipilimumab 5mg/ml

העדכונים העיקריים בעלון לרופא ובעלון לצרכן מפורטים בעמודים הבאים.

תוספת טקסט מסומנת בקו תחתון, מחיקת טקסט ~~בקו חוצה~~.

העלון לרופא והעלון לצרכן הנקיים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפסים על ידי פנייה לבעל הרישום בריסטול-מאיירס סקוויב (ישראל) בע"מ.

בברכה,

לנה גיטלין

מנהלת רגולציה ורוקחת ממונה

בריסטול-מאיירס סקוויב (ישראל)

עדכונים עיקריים בעלון לרופא:

[…..]

~~Patient safety information Card and Brochure~~

The marketing of Yervoy is subject to a risk management plan (RMP) including a ~~'~~patient ~~safety~~ pocket guide together with a patient wallet card (a safety information card)~~'. The 'patient safety information card' emphasizes~~ emphasizing important safety information that the patient should be aware of before and during treatment. Please ensure you are familiar with this important information and ~~advise~~ explain to the patient the need to review the patient pocket guide and the patient wallet card before starting treatment.

~~For patients receiving Yervoy in combination with Opdivo, please provide the patient with the 'Patient safety information card' and 'patient brochure' available for Opdivo in combination with Yervoy, and advise the patient to review it before starting treatment.~~

[…..]

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

~~The recommended dose of YERVOY as a single agent is 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a maximum of 4 doses. In the event of toxicity, doses may be delayed, but all treatment must be administered within 16 weeks of the first dose *[see Clinical Studies (14)]*.~~

The recommended dosage of YERVOY as a single agent is presented in Table 1.

Table 1: Recommended Dosages for YERVOY as a Single Agent

Indication	Recommended YERVOY Dosage	Duration of Therapy
Unresectable or metastatic melanoma	3 mg/kg every 3 weeks (90-minute intravenous infusion)	Maximum of 4 doses

The recommended dosages of YERVOY in combination with other therapeutic agents are presented in Table ~~1~~2. Refer to the respective Prescribing Information for each therapeutic agent administered in combination with YERVOY for recommended dosage information, as appropriate.

Table ~~1~~2: Recommended Dosages of YERVOY in Combination with Other Therapeutic Agents*

Indication	Recommended YERVOY Dosage	Duration of Therapy
Unresectable or metastatic melanoma	3 mg/kg every 3 weeks (90-minute intravenous infusion) with nivolumab 1 mg/kg (30-minute intravenous infusion on the same day)	In combination with nivolumab for a maximum of 4 doses or until unacceptable toxicity, whichever occurs earlier. After completing 4 doses of combination therapy, administer nivolumab as a single agent until disease progression or unacceptable toxicity.†
Advanced renal cell carcinoma	1 mg/kg every 3 weeks with nivolumab 3 mg/kg (30-minute intravenous infusion on the same day)	In combination with nivolumab for 4 doses. After completing 4 doses of combination therapy, administer nivolumab as single agent until disease progression or unacceptable toxicity†
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer	1 mg/kg every 3 weeks with nivolumab 3 mg/kg (30-minute intravenous infusion on the same day)	In combination with nivolumab for 4 doses. After completing 4 doses of combination therapy, administer nivolumab as single agent until disease progression or unacceptable toxicity†
Hepatocellular carcinoma	3 mg/kg every 3 weeks with nivolumab 1 mg/kg (30-minute intravenous infusion on the same day)	In combination with nivolumab for 4 doses. After completing 4 doses of combination therapy, administer nivolumab as single agent until disease progression or unacceptable toxicity†
Metastatic or recurrent non-small cell lung cancer	1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks (30-minute intravenous infusion) and histology-based platinum-doublet chemotherapy every 3 weeks	In combination with nivolumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression†
		2 cycles of histology-based platinum-doublet chemotherapy

Table ~~1~~2: Recommended Dosages of YERVOY in Combination with Other Therapeutic Agents*

Indication	Recommended YERVOY Dosage	Duration of Therapy
Malignant pleural mesothelioma	1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks (30-minute intravenous infusion) or 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks (30-minute intravenous infusion)	In combination with nivolumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression†

* Refer to the Prescribing Information for the agents administered in combination with YERVOY for recommended dosing information, as appropriate.

† Refer to the Prescribing Information for nivolumab for dosage information after completing use in combination with YERVOY.

~~**Recommended Dose Modifications**~~

2.2 Recommended Dosage Modifications for Adverse Reactions

No dose reduction for YERVOY is recommended. In general, withhold YERVOY for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue YERVOY for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, persistent moderate (Grade 2) or severe (Grade 3) reactions lasting 12 weeks or longer after last YERVOY dose (excluding endocrinopathy), or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids. Dosage modifications for YERVOY or YERVOY in combination with nivolumab for adverse reactions that require management different from these general guidelines are summarized in Table 3.

When YERVOY is administered in combination with nivolumab, withhold or permanently discontinue both YERVOY and nivolumab for toxicity.

~~**Table 2: Recommended Dosage Treatment Modifications for Immune-Mediated Adverse Reactions of YERVOY**~~

~~**Target/Organ System**~~	~~**Adverse Reaction (CTCAE v4)**~~	~~**Treatment Modification**~~
~~Endocrine~~	~~Symptomatic endocrinopathy~~	~~Withhold YERVOY~~ ~~Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0 to 1) and who are receiving less than 7.5 mg prednisone or equivalent per day.~~
	~~Symptomatic reactions lasting 6 weeks or longer~~	~~Permanently discontinue YERVOY~~

Table 2: Recommended Dosage Treatment Modifications for Immune-Mediated Adverse Reactions of YERVOY

Target/Organ System	**Adverse Reaction (CTCAE v4)**	**Treatment Modification**
	Inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day	
Ophthalmologic	Grade 2 through 4 reactions not improving to Grade 1 within 2 weeks while receiving topical therapy or requiring systemic treatment	Permanently discontinue YERVOY

~~**Table 2: Recommended Dosage Treatment Modifications for Immune-Mediated Adverse Reactions of YERVOY**~~

~~**Target/Organ System**~~	~~**Adverse Reaction (CTCAE v4)**~~	~~**Treatment Modification**~~
~~All Other~~	~~Grade 2~~	~~Withhold YERVOY~~ ~~Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0 to 1) and who are receiving less than 7.5 mg prednisone or equivalent per day.~~
	~~Grade 2 reactions lasting 6 weeks or longer~~ ~~Inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day~~ ~~Grade 3 or 4~~	~~Permanently discontinue YERVOY~~

Table 3: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	**Severity***	**Dosage Modifications**
Immune-Mediated Adverse Reactions *[See Warnings and Precautions (5.1)]*		
Colitis	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver or Hepatitis with tumor involvement of the liver/non-HCC	AST or ALT increases to more than 3 times and up to 5 times the ULN or Total bilirubin increases to more than 1.5 times and up to 3 times the ULN	Withhold[a]
	AST or ALT more than 5 times the ULN or Total bilirubin more than 3 times the ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[b]/HCC[c]	Baseline AST/ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST/ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to	Withhold[a]

Table 3: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modifications
	10 times ULN.	
	AST/ALT increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN.	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Endocrinopathies[d]	Grades 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Pneumonitis	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[a]
	Grade 4 increased blood creatinine	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Myocarditis	Grade 2, 3 or 4	Permanently discontinue
Ophthalmologic	Grade 2, 3, or 4 that does not improve to Grade 1 within 2 weeks while receiving topical therapy or that requires systemic treatment	Permanently discontinue
Other Adverse Reactions		
Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson Syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit of normal

* Based on Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03

[a] Resume in patients with complete or partial resolution (Grade 0 or 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.

[b] If AST/ALT are less than or equal to ULN at baseline, withhold or permanently discontinue YERVOY based on recommendations for hepatitis with no liver involvement.

[c] This guidance is only applicable to HCC patients who are being treated with YERVOY in combination with nivolumab.

[d] Depending on clinical severity, consider withholding for Grade 2 endocrinopathy until symptom improvement with hormone replacement. Resume once acute symptoms have resolved.

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8 USE IN SPECIFIC POPULATIONS

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8.4 Geriatric Use

Single Agent

Of the 511 patients treated with YERVOY in Study MDX010-20 (unresectable or metastatic melanoma), 28% were 65 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients.

In Combination with Nivolumab

Of the 314 patients randomized to YERVOY administered with nivolumab in CHECKMATE-067, 41% were 65 years or older and 11% were 75 years or older. No overall differences in safety or effectiveness were reported between elderly patients and younger patients.

~~CHECKMATE-142 (metastatic colorectal cancer) did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.~~

~~Of the 550 patients randomized to YERVOY 1 mg/kg with nivolumab in CHECKMATE-214 (renal cell carcinoma), 38% were 65 years or older and 8% were 75 years or older. No overall difference in safety was observed between these patients and younger patients. In geriatric patients with intermediate or poor risk, no overall difference in effectiveness was observed.~~

~~Of the 49 patients who received YERVOY 3 mg/kg with nivolumab in Cohort 4 of CHECKMATE-040 (hepatocellular carcinoma), 29% were between 65 years and 74 years of age and 8% were 75 years or older. Clinical studies of YERVOY in combination with nivolumab did not include sufficient numbers of patients with hepatocellular carcinoma aged 65 and over to determine whether they respond differently from younger patients.~~

Of the 303 patients randomized to YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-743 (malignant pleural mesothelioma), 77% were 65 years old or older and 26% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there were higher rates of serious adverse reactions and discontinuation rate due to adverse reactions in patients aged 75 years or older (68% and 35%, respectively) relative to all patients who received YERVOY with nivolumab (54% and 28%, respectively). For patients aged 75 years or older who received chemotherapy, the rate of serious adverse reactions was 34% and discontinuation due to adverse reactions was 26% relative to 28% and 19% respectively for all patients. The hazard ratio for overall survival was 0.76 (95% CI: 0.52, 1.11) in the 71 patients younger than 65 years compared to 0.74 (95% CI: 0.59, 0.93) in the 232 patients 65 years or older randomized to YERVOY in combination with nivolumab. The hazard ratio for overall survival was 0.67 (95% CI: 0.54, 0.84) in the patients younger than 75 years compared to 1.01 (95% CI: 0.70, 1.47) in the patients 75 years or older randomized to Yervoy in combination with nivolumab.

Of the 550 patients randomized to YERVOY 1 mg/kg with nivolumab in CHECKMATE-214 (renal cell carcinoma), 38% were 65 years or older and 8% were 75 years or older. No overall difference in safety was observed between these patients and younger patients. In geriatric patients with intermediate or poor risk, no overall difference in effectiveness was observed.

Of the 49 patients who received YERVOY 3 mg/kg with nivolumab in Cohort 4 of CHECKMATE-040 (hepatocellular carcinoma), 29% were between 65 years and 74 years of age and 8% were 75 years or older. Clinical studies of YERVOY in combination with nivolumab did not include sufficient numbers of patients with hepatocellular carcinoma aged 65 and over to determine whether they respond differently from younger patients.

CHECKMATE-142 (metastatic colorectal cancer) did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

In Combination with Nivolumab and Platinum-Doublet Chemotherapy

Of the 361 patients randomized to YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 360 mg every 3 weeks and platinum-doublet chemotherapy every 3 weeks (for 2 cycles) in CHECKMATE-9LA (NSCLC), 51% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (43%) relative to all patients who received YERVOY with nivolumab and chemotherapy (24%). For patients aged 75 years or older who received chemotherapy only, the discontinuation rate due to adverse reactions was 16% relative to all patients who had a

discontinuation rate of 13%. Based on an updated analysis for overall survival, of the 361 patients randomized to YERVOY in combination with nivolumab and platinum-doublet chemotherapy in CHECKMATE-9LA, the hazard ratio for overall survival was 0.61 (95% CI: 0.47, 0.80) in the 176 patients younger than 65 years compared to 0.73 (95% CI: 0.56, 0.95) in the 185 patients 65 years or older.

~~Of the 303 patients randomized to YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-743 (malignant pleural mesothelioma), 77% were 65 years old or older and 26% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there were higher rates of serious adverse reactions and discontinuation rate due to adverse reactions in patients aged 75 years or older (68% and 35%, respectively) relative to all patients who received YERVOY with nivolumab (54% and 28%, respectively). For patients aged 75 years or older who received chemotherapy, the rate of serious adverse reactions was 34% and discontinuation due to adverse reactions was 26% relative to 28% and 19% respectively for all patients. The hazard ratio for overall survival was 0.76 (95% CI: 0.52, 1.11) in the 71 patients younger than 65 years compared to 0.74 (95% CI: 0.59, 0.93) in the 232 patients 65 years or older randomized to YERVOY in combination with nivolumab. The hazard ratio for overall survival was 0.67 (95% CI: 0.54, 0.84) in the patients younger than 75 years compared to 1.01 (95% CI: 0.70, 1.47) in the patients 75 years or older randomized to Yervoy in combination with nivolumab.~~

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עדכונים עיקריים בעלון לצרכן:

[.....]

מדריך כיס וכרטיס ~~וחוברת~~ מידע בטיחותי למטופל

בנוסף לעלון, לתכשיר יירבוי ~~קיים~~ קיימים מדריך כיס וכרטיס מידע בטיחותי למטופל.
מדריך הכיס והכרטיס ~~זה~~ מכילים מידע בטיחותי חשוב שעליך לדעת לפני התחלת הטיפול ובמהלך הטיפול ביירבוי ולפעול על פיהם~~:~~. יש לעיין במדריך הכיס, בכרטיס ובעלון לצרכן בטרם תחילת השימוש בתכשיר. יש לשמור את הכרטיס ומדריך הכיס לעיון נוסף במידת הצורך.

~~אם הרופא המטפל רשם לך יירבוי בטיפול משולב יחד עם אופדיבו (ניבולומאב), קיימים כרטיס וחוברת מידע בטיחותי למטופל עבור הטיפול המשולב. הכרטיס והחוברת מכילים מידע בטיחותי חשוב שעליך לדעת לפני התחלת הטיפול ובמהלך הטיפול ביירבוי בשילוב עם אופדיבו, ולפעול על פיהם. יש לעיין בחומרים אלו ובעלון לצרכן בטרם תחילת השימוש בתכשיר. יש לשמור את הכרטיס והחוברת לעיון נוסף במידת הצורך.~~

[.....]

2. לפני השימוש בתרופה:

[.....]

היריון והנקה:
יירבוי עלולה להזיק לעובר.

נשים היכולות להרות:
- הרופא המטפל יערוך לך בדיקת היריון לפני תחילת הטיפול ביירבוי.
- עלייך להשתמש באמצעי-מניעה יעיל במהלך הטיפול ובמשך 3 חודשים לפחות לאחר מתן ~~המנה~~ מנת יירבוי האחרונה שלך~~של יירבוי~~. שוחחי עם הרופא על אמצעי המניעה שבהם את יכולה להשתמש בפרק זמן זה.
- דווחי לרופא המטפל באופן מיידי אם נכנסת להיריון או אם הינך חושבת שאת בהיריון במהלך הטיפול ביירבוי.

הנקה:
- דווחי לרופא המטפל אם הינך מניקה או מתכננת להניק. לא ידוע אם יירבוי יכולה לעבור לחלב אם.
- אל תניקי במהלך הטיפול ביירבוי וכן במשך 3 חודשים לאחר ~~המנה~~ מנת יירבוי האחרונה שלך ~~יירבוי~~.

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6. מידע נוסף:

[.....]

כיצד נראית התרופה ומה תוכן האריזה:
נוזל צלול עד חלבי במקצת וחסר צבע עד גוון צהבהב במקצת. הנוזל עשוי להכיל חלקיקים ~~קלים~~ (מעטים).
יירבוי זמינה בבקבוקון לשימוש חד-פעמי של 10 מ"ל (50 מ"ג) ובבקבוקון לשימוש חד-פעמי של 40 מ"ל (200 מ"ג).

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