מאי 2019

Yervoy (Ipilimumab) 5 mg/ml

Concentrate for solution for infusion

רופא/ה ,רוקח/ת יקר/ה,

ברצוננו להודיעך על עדכון בעלון לרופא של התכשיר **יירבוי** (איפילימומאב) בישראל.

התוויות התכשיר כפי שאושרו ע"י משה"ב:

Yervoy (ipilimumab) is indicated for the treatment of advanced (unresectable or metastatic) melanoma.

Yervoy in combination with Opdivo (nivolumab) is indicated for the treatment of patient with advanced (unresectable or metastatic) melanoma.

בפירוט שלהלן כלולים העדכונים המהותיים בלבד (טקסט שנוסף מסומן בצבע אדום ובקו תחתון וטקסט שהוסר מסומן בצבע אדום ~~ובקו אמצעי~~).
למידע מלא על התרופה יש לעיין בעלון לרופא כפי שאושר על ידי משרד הבריאות.

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס על ידי פנייה לבעל הרישום בריסטול- מאיירס סקוויב (ישראל) בע"מ.

בכבוד רב,
מיכל ניר ורדימון
מנהלת רגולציה

עדכונים מהותיים בעלון לרופא:

4 CONTRAINDICATIONS

Hypersensitivity to ipilimumab or to any of the excipients listed in section 11 (Description).
~~None.~~

5 WARNINGS AND PRECAUTIONS

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5.1 Immune-Mediated Enterocolitis/Colitis

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5.3 Immune-Mediated Dermatitis/Skin Adverse Reactions

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~~Caution should be used when considering the use of YERVOY in a patient who has previously experienced a severe or life-threatening skin adverse reaction on a prior cancer immune-stimulatory therapy.~~

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5.6 Immune-Mediated Pneumonitis

Immune-mediated pneumonitis, including fatal cases, can occur with nivolumab with YERVOY. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or more severe (Grade 3-4) pneumonitis, followed by corticosteroid taper. Withhold YERVOY dosing in patients with moderate to severe signs and symptoms. Permanently discontinue YERVOY for life-threatening (Grade 4) pneumonitis *[see Dosage and Administration (2.2)]*.

5.7 Immune-Mediated Nephritis and Renal Dysfunction

Immune-mediated nephritis can occur with nivolumab with YERVOY. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) increased serum creatinine. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or severe (Grade 3) increased serum creatinine, if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents. Withhold YERVOY dosing in patients with moderate to severe signs and symptoms. Permanently discontinue YERVOY for life-threatening (Grade 4) increased serum creatinine *[see Dosage and Administration (2.2)]*.

5.8 Immune-Mediated Encephalitis

Immune-mediated encephalitis can occur with YERVOY. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

Withhold YERVOY in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue YERVOY for immune-mediated encephalitis *[see Dosage and Administration (2.2)]*.

5.9 Infusion Reactions

Severe infusion reactions can occur with nivolumab with YERVOY. Discontinue YERVOY in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions *[see Dosage and Administration (2.2)]*.

~~5.4~~5.10 Other Immune-Mediated Adverse Reactions, Including Ocular Manifestations

~~The following clinically significant immune-mediated adverse reactions were seen in less than 1% of YERVOY-treated patients in Study 1: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia.~~

~~Across the clinical development program for YERVOY, the following likely immune-mediated adverse reactions were also reported with less than 1% incidence: myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, autoimmune thyroiditis, sarcoidosis, neurosensory hypoacusis, autoimmune central neuropathy (encephalitis), myositis, polymyositis, and ocular myositis.~~

YERVOY as a Single Agent

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Monitor patients for signs or symptoms of ocular toxicity, which may include blurred vision and reduced visual acuity. Immune-mediated ocular toxicity may be associated with retinal detachment or permanent vision loss. Administer corticosteroid eye drops to patients who develop uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy. *[See Dosage and Administration (2.~~2~~3).]* If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving YERVOY and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Metastatic Melanoma

In MDX010-20, the following clinically significant immune-mediated adverse reactions were seen in less than 1% of YERVOY-treated patients: cytopenias, nephritis, pneumonitis, meningitis, pericarditis, uveitis, and iritis.

Other Clinical Experience

Across 21 dose-ranging trials administering YERVOY at doses of 0.1 to 20 mg/kg (n=2478), the following likely immune-mediated adverse reactions were also reported with less than 1% incidence unless specified: angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, iritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, arthritis, autoimmune thyroiditis, neurosensory hypoacusis, autoimmune central neuropathy (encephalitis), myositis, polymyositis, ocular myositis, cytopenias (2.5%), and nephritis. Also observed pancreatitis, sarcoidosis and fatal myocarditis.

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5.12 Risks Associated When Administered in Combination with Nivolumab

When YERVOY is administered in combination with nivolumab, refer to the nivolumab prescribing information for additional risk information that applies to the combination use.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Immune-mediated enterocolitis/colitis *[see Warnings and Precautions (5.1)]*.
- Immune-mediated hepatitis *[see Warnings and Precautions (5.2)]*.
- Immune-mediated dermatitis/skin adverse reactions *[see Warnings and Precautions (5.3)]*.
- Immune-mediated neuropathies *[see Warnings and Precautions (5.4)]*.
- Immune-mediated endocrinopathies *[see Warnings and Precautions (5.5)]*.
- *Immune-mediated pneumonitis [see Warnings and Precautions (5.6)].*
- *Immune-mediated nephritis and renal dysfunction [see Warnings and Precautions (5.7)].*
- *Immune-mediated encephalitis [see Warnings and Precautions (5.8)].*
- *Infusion reactions [see Warnings and Precautions (5.9)].*
- Other immune-mediated adverse reactions, including ocular manifestations *[see Warnings and Precautions (5.~~6~~10)]*.
- Embryo-fetal toxicity *[see Warnings and Precautions (5.11)].*

In patients receiving YERVOY 3 mg/kg for unresectable or metastatic melanoma in MDX010-20 ~~Trial 1~~, 15% of patients receiving monotherapy and 12% of patients treated in combination with gp100 peptide vaccine experienced Grade 3 to 5 immune-mediated reactions.

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6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ipilimumab in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

Eleven (1.1%) of 1024 evaluable patients with unresectable or metastatic melanoma tested positive for treatment-emergent binding antibodies against ipilimumab (TE-ADAs) in an electrochemiluminescent (ECL) based assay. This assay had substantial limitations in detecting anti-ipilimumab antibodies in the presence of ipilimumab. Seven (4.9%) of 144 patients receiving ipilimumab and 7 (4.5%) of 156 patients receiving placebo for the adjuvant treatment of melanoma tested positive for TE-ADAs using an ECL assay with improved drug tolerance. No patients tested positive for neutralizing antibodies. No infusion-related reactions occurred in patients who tested positive for TE-ADAs.

~~Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to ipilimumab with the incidences of antibodies to other products may be misleading.~~

8 USE IN SPECIFIC POPULATIONS

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8.2 Lactation

Risk Summary

It is not known whether YERVOY is present~~secreted~~ in human milk. In monkeys, ipilimumab was present in milk (see Data). ~~.~~ There are no data to assess the effects of YERVOY on milk production. Advise women to discontinue breastfeeding~~nursing~~ during treatment with YERVOY and for 3 months following the final dose.

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8.5 Geriatric Use

Of the 511 patients treated with YERVOY in MDX010-20 (unresectable or metastatic melanoma) ~~at 3 mg/kg (trial 1)~~, 28% were 65 years and over. No overall differences in safety or efficacy were reported between the elderly patients (65 years and over) and younger patients (less than 65 years).

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16 HOW SUPPLIED/STORAGE AND HANDLING

YERVOY (ipilimumab) Injection is available as follows:

Carton Contents
One 50 mg vial (5 mg/mL), single-use vial
One 200 mg vial (5 mg/mL), single-use vial

Store YERVOY under refrigeration at 2°C to 8°C .~~Do not freeze.~~ Protect YERVOY~~vials~~ from light~~.~~ by storing in the original carton until time of use. Do not freeze or shake.

The expiry date of the product is indicated on the packaging materials.