הודעה על החמרה (מידע בטיחות) בעלון לרופא

(מעודכן 05.2013)

תאריך 24.1.2016

שם תכשיר באנגלית ומספר רישום Yervoy #147-62-33522

שם בעל הרישום BRISTOL-MYERS SQUIBB (ISRAEL)

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות

פרק בעלון	טקסט נוכחי	טקסט חדש
RECOMMENDED DOSE MODIFICATIONS	• Withhold scheduled dose of YERVOY for any moderate immune-mediated adverse reactions or for symptomatic endocrinopathy. For patients with complete or partial resolution of adverse reactions (Grade 0–1), and who are receiving less than 7.5 mg prednisone or equivalent per day, resume YERVOY at a dose of 3 mg/kg every 3 weeks until administration of all 4 planned doses or 16 weeks from first dose, whichever occurs earlier. • Permanently discontinue YERVOY for any of the following: o Persistent moderate adverse reactions or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day. o Failure to complete full treatment course within 16 weeks from administration of first dose. o Severe or life-threatening adverse reactions, including any of the following: ▪ Colitis with abdominal pain, fever, ileus, or	**Table 1: Recommended Treatment Modifications for Immune-Mediated Adverse Reactions of YERVOY** **Target/Organ System** / **Adverse Reaction (CTCAE v3)** / **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 • Inability to reduce corticosteroid dose to 7.5 mg / Permanently discontinue YERVOY

	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
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

peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times the upper limit of normal or total bilirubin >3 times the upper limit of normal
- Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations
- Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
- Severe immune-mediated reactions involving any organ system (eg, nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)
- Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy

Immune-mediated Dermatitis …… Permanently discontinue YERVOY in patients with Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations. Administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month. Withhold YERVOY dosing in patients with moderate to severe signs and symptoms. [See Dosage and Administration (2.2).] 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. ….. **Immune-Mediated Endocrinopathies** …… Monitor clinical chemistries, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at the start of treatment, before each dose, and as clinically indicated based on symptoms. …	**5.3 Immune-mediated Dermatitis** …… Permanently discontinue YERVOY in patients with Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations. Administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month. Withhold YERVOY dosing in patients with moderate to severe signs and symptoms. [See Dosage and Administration (2.2).] ….. **Immune-Mediated Endocrinopathies** …… Monitor clinical chemistries and thyroid function tests at the start of treatment, before each dose, and as clinically indicated based on symptoms. ……	WARNINGS AND PRECAUTION

Other Immune-Mediated Adverse Reactions, Including Ocular Manifestations ….. 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: 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, hemolytic anemia, and nephritis. ….. **Embryo-fetal Toxicity** Based on its mechanism of action and data from animal studies, YERVOY can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner. The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with a YERVOY-containing regimen and for 3 months after the last dose of YERVOY *[see Use in Specific Populations (8.1, 8.3)]*.	**Other Immune-Mediated Adverse Reactions, Including Ocular Manifestations** …. 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. …..	

Postmarketing Experience The following adverse reactions have been identified during postapproval use of YERVOY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Skin and Subcutaneous Tissue Disorders:* Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)	…	ADVERSE REACTIONS
Lactation Risk Summary It is not known whether YERVOY is secreted in human milk. In monkeys, ipilimumab was present in milk. There are no data to assess the effects of YERVOY on milk production. Advise women to discontinue nursing during treatment with YERVOY and for 3 months following the final dose. **Females and Males of Reproductive Potential** Contraception Based on its mechanism of action, YERVOY can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with YERVOY and for 3 months following the last dose of YERVOY.	**Pregnancy** **Pregnancy Category C** There are no adequate and well-controlled studies of YERVOY in pregnant women. Use YERVOY during pregnancy only if the potential benefit justifies the potential risk to the fetus. In a combined study of embryo-fetal and peri-postnatal development, pregnant cynomolgus monkeys received ipilimumab every 3 weeks from the onset of organogenesis in the first trimester through parturition, at exposure levels either 2.6 or 7.2 times higher by AUC than the exposures at the clinical dose of 3 mg/kg of ipilimumab. No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, the ipilimumab -treated groups experienced higher	USE IN SPECIFIC POPULATIONS

incidences of severe toxicities including abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner compared to controls. *[See Nonclinical Toxicology (13.2).]*

Human IgG1 is known to cross the placental barrier and ipilimumab is an IgG1; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus.

Nursing Mothers

It is not known whether ipilimumab is secreted in human milk. In monkeys treated at dose levels resulting in exposures 2.6 and 7.2 times higher than those in humans at the recommended dose, ipilimumab was present in milk at concentrations of 0.1 and 0.4 mcg/mL, representing a ratio of up to 0.3% of the serum concentration of the drug. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from YERVOY, a decision should be made whether to discontinue nursing or to discontinue YERVOY, taking into account the importance of YERVOY to the mother.

Immune-Mediated Adverse Reactions Inform patients of the potential risk of immune-mediated adverse reactions *[see Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5, 5.6)]*. **Embryo-fetal Toxicity** Advise female patients that YERVOY can cause fetal harm. Advise females of reproductive potential to use effective contraception during treatment with YERVOY and for 3 months after the last dose. Advise female patients to contact their healthcare provider with a known or suspected pregnancy. **Lactation** Advise women not to breastfeed during treatment with YERVOY and for 3 months after the last dose *[see Use in Specific Populations (8.2)]*.	• Inform patients of the potential risk of immune-mediated adverse reactions. • Advise women that YERVOY may cause fetal harm. • Advise nursing mothers not to breastfeed while taking YERVOY.	PATIENT COUNSELING INFORMATION

מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב.
שינויים שאינם בגדר החמרות סומנו (בעלון) בצבע שונה. יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.
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