פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר ע"י משרד הבריאות בתאריך אוגוסט 2017, ועודכן בהתאם להוראות משרד הבריאות בתאריך אפריל 2019

FULL PRESCRIBING INFORMATION

NAME OF THE MEDICINAL PRODUCT

YERVOY 5 MG/ML

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 5 mg ipilimumab.

One 10 ml vial contains 50 mg of ipilimumab.

One 40 ml vial contains 200 mg of ipilimumab.

PHARMACEUTICAL FORM

Concentrate for solution for infusion

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

YERVOY can result in severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions. ***[See Dosage and Administration (2.2).]***

Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at baseline and before each dose. ***[See Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5).]***

1 INDICATIONS AND USAGE

- 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

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)]*.

YERVOY (ipilimumab), in combination with OPDIVO (nivolumab).

Review the Full Prescribing Information for OPDIVO (nivolumab) prior to initiation.

Recommended Dose Modifications

Table 1: Recommended 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 □ Inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day	Permanently discontinue YERVOY
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 1: Recommended 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

2.2 Preparation and Administration

- Do not shake product.
- Inspect parenteral drug products visually for particulate matter and discoloration prior to administration. Discard vial if solution is cloudy, there is pronounced discoloration (solution may have pale-yellow color), or there is foreign particulate matter other than translucent-to-white, amorphous particles.

Preparation of Solution

- Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
- Withdraw the required volume of YERVOY and transfer into an intravenous bag.
- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.
- Store the diluted solution for no more than 24 hours under refrigeration (2°C to 8°C).
- Discard partially used vials or empty vials of YERVOY.

Administration Instructions

- Do not mix YERVOY with, or administer as an infusion with, other medicinal products.
- Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after each dose.

  Administer diluted solution over 90 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.

3 DOSAGE FORMS AND STRENGTHS

Injection: 50 mg/10 mL (5 mg/mL)
Injection: 200 mg/40 mL (5 mg/mL)

4 CONTRAINDICATIONS

Hypersensitivity to ipilimumab or to any of the excipients listed in section 11 (Description).

5 WARNINGS AND PRECAUTIONS

YERVOY can result in severe and fatal immune-mediated reactions. *[See Boxed Warning.]*

5.1 Immune-Mediated Enterocolitis/Colitis

Immune-mediated enterocolitis, including fatal cases, can occur with YERVOY.

Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms.

Permanently discontinue YERVOY in patients with severe enterocolitis and initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. In clinical trials, rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients. Consider adding anti-TNF or other immunosuppressant agents for management of immune-mediated enterocolitis unresponsive to systemic corticosteroids within 3 to 5 days or recurring after symptom improvement.

Withhold YERVOY dosing for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for more than 1 week, initiate systemic corticosteroids at a dose of 0.5 mg/kg/day prednisone or equivalent *[see Dosage and Administration (2.2)]*.

YERVOY as a Single Agent

Metastatic Melanoma

In patients receiving YERVOY 3 mg/kg in MDX010-20 (NCT00094653), , severe, life-threatening, or fatal (diarrhea of 7 or more stools above baseline, fever, ileus, peritoneal signs; Grade 3 to 5) immune-mediated enterocolitis occurred in 34 YERVOY-treated patients (7%), and moderate (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) enterocolitis occurred in 28 YERVOY-treated patients (5%). Across all YERVOY-treated patients (n=511), 5 patients (1%) developed intestinal perforation, 4 patients

(0.8%) died as a result of complications, and 26 patients (5%) were hospitalized for severe enterocolitis.

The median time to onset of Grade 3 to 5 enterocolitis was 1.7 months (range: 11 days to 3.1 months) and for Grade 2 enterocolitis was 1.4 months (range: 2 days to 4.3 months).

Twenty-nine patients (85%) with Grade 3 to 5 enterocolitis were treated with high-dose (≥40 mg prednisone equivalent per day) corticosteroids, with a median dose of 80 mg/day of prednisone or equivalent; the median duration of treatment was 16 days (ranging up to 3.2 months) followed by corticosteroid taper. Of the 28 patients with moderate enterocolitis, 46% were not treated with systemic corticosteroids, 29% were treated with <40 mg prednisone or equivalent per day for a median duration of 1.2 months, and 25% were treated with high-dose corticosteroids for a median duration of 10 days prior to corticosteroid taper. Infliximab was administered to 5 (8%) of the 62 patients with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids.

Of the 34 patients with Grade 3 to 5 enterocolitis, 74% experienced complete resolution, 3% experienced improvement to Grade 2 severity, and 24% did not improve. Among the 28 patients with Grade 2 enterocolitis, 79% experienced complete resolution, 11% improved, and 11% did not improve.

5.2 Immune-Mediated Hepatitis

Immune-mediated hepatitis, including fatal cases, can occur with YERVOY.

Monitor liver function tests (hepatic transaminase and bilirubin levels) and assess patients for signs and symptoms of hepatotoxicity before each dose of YERVOY. In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of liver function test monitoring until resolution.

Permanently discontinue YERVOY in patients with Grade 3 to 4 hepatotoxicity and administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When liver function tests show sustained improvement or return to baseline, initiate corticosteroid tapering and continue to taper over 1 month. Across the clinical development program for YERVOY, mycophenolate treatment has been administered in patients who have persistent severe hepatitis despite high-dose corticosteroids. Withhold YERVOY in patients with Grade 2 hepatotoxicity *[see Dosage and Administration (2.2)]*.

YERVOY as a Single Agent

Metastatic Melanoma

In patients receiving YERVOY 3 mg/kg in MDX010-20 „ severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations of more than 5 times the upper limit of normal or total bilirubin elevations more than 3 times the upper limit of normal; Grade 3 to 5) occurred in 8 YERVOY-treated patients (2%), with fatal hepatic failure in 0.2% and hospitalization in 0.4% of YERVOY-treated patients. An additional 13 patients (2.5%) experienced moderate hepatotoxicity manifested by liver function test abnormalities (AST or ALT elevations of more

than 2.5 times but not more than 5 times the upper limit of normal or total bilirubin elevation of more than 1.5 times but not more than 3 times the upper limit of normal; Grade 2). The underlying pathology was not ascertained in all patients but in some instances included immune-mediated hepatitis. There were insufficient numbers of patients with biopsy-proven hepatitis to characterize the clinical course of this event.

Concurrent Administration with Vemurafenib

In a dose-finding trial, Grade 3 increases in transaminases with or without concomitant increases in total bilirubin occurred in 6 of 10 patients who received concurrent YERVOY (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID).

5.3 Immune-Mediated Dermatitis/Skin Adverse Reactions

Immune-mediated dermatitis, including fatal cases, can occur with YERVOY.

Monitor patients for signs and symptoms of dermatitis, such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated.

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)]*.

For mild to moderate dermatitis, such as localized rash and pruritus, treat symptomatically. Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.

YERVOY as a Single Agent

Metastatic Melanoma

In patients receiving YERVOY 3 mg/kg in MDX010-20, severe, life-threatening, or fatal immune-mediated dermatitis (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3to 5) occurred in 13 YERVOY-treated patients (2.5%). One patient (0.2%) died as a result of toxic epidermal necrolysis and one additional patient required hospitalization for severe dermatitis. There were 63 patients (12%) with moderate (Grade 2) dermatitis.

The median time to onset of moderate, severe, or life-threatening immune-mediated dermatitis was 22 days and ranged up to 4.0 months from the initiation of YERVOY.

Seven YERVOY-treated patients (54%) with severe dermatitis received high-dose corticosteroids (median dose 60 mg prednisone/day or equivalent) for up to 3.4 months followed

by corticosteroid taper. Of these 7 patients, 6 had complete resolution; time to resolution ranged up to 3.6 months.

Of the 63 patients with moderate dermatitis, 25 (40%) were treated with systemic corticosteroids (median of 60 mg/day of prednisone or equivalent) for a median of 15 days, 7 (11%) were treated with only topical corticosteroids, and 31 (49%) did not receive systemic or topical corticosteroids. Forty-four patients (70%) with moderate dermatitis were reported to have complete resolution, 7 (11%) improved to mild (Grade 1) severity, and 12 (19%) had no reported improvement.

5.4 Immune-Mediated Neuropathies

Immune-mediated neuropathies, including fatal cases, can occur with YERVOY.

Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Permanently discontinue YERVOY in patients with severe neuropathy (interfering with daily activities) such as Guillain-Barré-like syndromes. Institute medical intervention as appropriate for management of severe neuropathy. Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe neuropathies. Withhold YERVOY dosing in patients with moderate neuropathy (not interfering with daily activities) [*see Dosage and Administration (2.2)]*.

YERVOY as a Single Agent

Metastatic Melanoma

In patients receiving YERVOY 3 mg/kg in MDX010-20, 1 case of fatal Guillain-Barré syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported. Across the clinical development program of YERVOY, myasthenia gravis and additional cases of Guillain-Barré syndrome have been reported.

5.5 Immune-Mediated Endocrinopathies

Immune-mediated endocrinopathies, including life-threatening cases, can occur with YERVOY.

Monitor patients for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-mediated.

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. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland.

Withhold YERVOY dosing in symptomatic patients and consider referral to an endocrinologist. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent, and initiate appropriate hormone replacement therapy. *[See Dosage and Administration (2.2).]*

YERVOY as a Single Agent

Metastatic Melanoma

In patients receiving YERVOY 3 mg/kg in MDX010-20, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3to 4) occurred in 9 YERVOY-treated patients (1.8%). All 9 patients had hypopituitarism and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies. Moderate endocrinopathy (requiring hormone replacement or medical intervention; Grade 2) occurred in 12 patients (2.3%) and consisted of hypothyroidism, adrenal insufficiency, hypopituitarism, and 1 case each of hyperthyroidism and Cushing's syndrome.

The median time to onset of moderate to severe immune-mediated endocrinopathy was 2.5 months and ranged up to 4.4 months after the initiation of YERVOY.

Of the 21 patients with moderate to life-threatening endocrinopathy, 17 patients required long-term hormone replacement therapy including, most commonly, adrenal hormones (n=10) and thyroid hormones (n=13).

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)]*.

5.10 Other Immune-Mediated Adverse Reactions, Including Ocular Manifestations

YERVOY as a Single Agent

Permanently discontinue YERVOY for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe immune-mediated adverse reactions.

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 (2.3).]* 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.

5.11 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)]*.

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 (5.10)]*.
- Embryo-fetal toxicity *[see Warnings and Precautions (5.11)]*.

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

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared with rates in other clinical trials or experience with therapeutics in the same class and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to YERVOY 3 mg/kg as a single agent in MDX010 20, a randomized trial in

patients with unresectable or metastatic melanoma to YERVOY 10 mg/kg as a single agent in CA184-029, a randomized trial in patients with resected Stage IIIA (>1 mm nodal involvement), IIIB, and IIIC (with no in-transit metastases) cutaneous melanoma.

Clinically significant adverse reactions were evaluated in a total of 982 patients treated in MDX010-20 and CA184-029 and in 21 dose-ranging trials (n=2478) administering YERVOY at doses of 0.1 to 20 mg/kg [see *Warnings and Precautions (5.6)]*.

Unresectable or Metastatic Melanoma

The safety of YERVOY was evaluated in MDX010-20, a randomized, double-blind clinical trial in which 643 previously treated patients with unresectable or metastatic melanoma received YERVOY 3 mg/kg for 4 doses given by intravenous infusion as a single agent (n=131), YERVOY with an investigational gp100 peptide vaccine (gp100) (n=380), or gp100 peptide vaccine as a single agent (n=132) *[see Clinical Studies (14.1)]*. Patients in the trial received a median of 4 doses (range: 1 to 4 doses).

MDX010-20 excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation.

The trial population characteristics were: median age 57 years (range: 19 to 90), 59% male, 94% white, and baseline ECOG performance status 0 (56%).

YERVOY was discontinued for adverse reactions in 10% of patients.

Table 2 presents selected adverse reactions from MDX010-20, which occurred in at least 5% of patients in the YERVOY-containing arms and with at least 5% increased incidence over the control gp100 arm for all-grade events and at least 1% incidence over the control group for Grade 3 to 5 events.

Table 2: Selected Adverse Reactions in MDX010-20

	Percentage (%) of Patients[a]					
	YERVOY 3 mg/kg n=131		YERVOY 3 mg/kg+gp100 n=380		gp100 n=132	
System Organ Class/ Preferred Term	Any Grade	Grade 3to 5	Any Grade	Grade 3to 5	Any Grade	Grade 3to 5
General Disorders and Administration Site Conditions						
Fatigue	41	7	34	5	31	3
Gastrointestinal Disorders						
Diarrhea	32	5	37	4	20	1
Colitis	8	5	5	3	2	0
Skin and Subcutaneous Tissue Disorders						
Pruritus	31	0	21	<1	11	0
Rash	29	2	25	2	8	0

[a] Incidences presented in this table are based on reports of adverse events regardless of causality.

Table 3 presents the per-patient incidence of severe, life-threatening, or fatal immune-mediated adverse reactions fromMDX010-20.

Table 3: Severe to Fatal Immune-Mediated Adverse Reactions in MDX010-20

	Percentage (%) of Patients	
	YERVOY 3 mg/kg n=131	YERVOY 3 mg/kg+gp100 n=380
Any Immune-Mediated Adverse Reaction	15	12
Enterocolitis[a,b]	7	7
Hepatotoxicity[a]	1	2
Dermatitis[a]	2	3
Neuropathy[a]	1	<1
Endocrinopathy	4	1
Hypopituitarism	4	1
Adrenal insufficiency	0	1
Other		
Pneumonitis	0	<1
Meningitis	0	<1
Nephritis	1	0
Eosinophilia[c]	1	0
Pericarditis[a,c]	0	<1

[a] Including fatal outcome.

[b] Including intestinal perforation.
[c] Underlying etiology not established.

Other Clinical Experience

Across clinical studies that utilized YERVOY doses ranging from 0.3 to 10 mg/kg, the following adverse reactions were also reported (incidence less than 1% unless otherwise noted): urticaria (2%), large intestinal ulcer, esophagitis, acute respiratory distress syndrome, renal failure, and infusion reaction.

Adverse reactions in patients with advanced melanoma treated with ipilimumab 3 mg/kg (n= 767). Frequencies are based on pooled data from 9 clinical trials investigating the ipilimumab 3 mg/kg dose in melanoma.

Common: headache, weight decreased;
Very common: fatigue, pyrexia, vomiting, nausea, decreased appetite

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval 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)

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

7 DRUG INTERACTIONS

No formal pharmacokinetic drug interaction studies have been conducted with YERVOY.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.1.1 Risk Summary

Based on data from animal studies and its mechanism of action, YERVOY can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. 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 *[see Data]*. The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. 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. There is insufficient human data for YERVOY exposure in pregnant women. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.1.2 Data

8.1.2.1 Animal Data

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. No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, administration of ipilimumab at doses resulting in exposures approximately 2.6 to 7.2 times the human exposure at a dose of 3 mg/kg resulted in dose-related increases in abortion, stillbirth, premature delivery (with corresponding lower birth weight), and an increased incidence of infant mortality. In addition, developmental abnormalities were identified in the urogenital system of 2 infant monkeys exposed *in utero* to 30 mg/kg of ipilimumab (7.2 times the AUC in humans at the

3 mg/kg dose). One female infant monkey had unilateral renal agenesis of the left kidney and ureter, and 1 male infant monkey had an imperforate urethra with associated urinary obstruction and subcutaneous scrotal edema.

Genetically engineered mice heterozygous for CTLA-4 (CTLA-4+/−), the target for ipilimumab, appeared healthy and gave birth to healthy CTLA-4+/− heterozygous offspring. Mated CTLA-4+/− heterozygous mice also produced offspring deficient in CTLA-4 (homozygous negative, CTLA-4−/−). The CTLA-4−/− homozygous negative offspring appeared healthy at birth, exhibited signs of multiorgan lymphoproliferative disease by 2 weeks of age, and all died by 3 to 4 weeks of age with massive lymphoproliferation and multiorgan tissue destruction.

8.2 Lactation

Risk Summary

It is not known whether YERVOY is presentin 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 during treatment with YERVOY and for 3 months following the final dose.

Data

In monkeys treated at dose levels resulting in exposures 2.6 and 7.2 times higher than those in humans at a 3 mg/kg dose, ipilimumab was present in milk at concentrations of 0.1 mcg/mL and 0.4 mcg/mL, representing a ratio of up to 0.3% of the steady-state serum concentration of the drug.

8.3 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.

8.4 Pediatric Use

Safety and effectiveness of YERVOY have not been established in pediatric patients.

8.5 Geriatric Use

Of the 511 patients treated with YERVOY in MDX010-20 (unresectable or metastatic melanoma) , 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).

8.6 Renal Impairment

No dose adjustment is needed for patients with renal impairment. *[See Clinical Pharmacology (12.3).]*

8.7 Hepatic Impairment

No dose adjustment is needed for patients with mild hepatic impairment (total bilirubin [TB] >1.0 to 1.5 times the upper limit of normal [ULN] or AST >ULN). YERVOY has not been studied in patients with moderate (TB >1.5 × to 3.0 times ULN and any AST) or severe (TB >3 times ULN and any AST) hepatic impairment. *[See Clinical Pharmacology (12.3).]*

10 OVERDOSAGE

There is no information on overdosage with YERVOY.

11 DESCRIPTION

Ipilimumab is a recombinant, human monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Ipilimumab is an IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. Ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture.

YERVOY is a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow solution for intravenous infusion, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. It is supplied in single-use vials of 50 mg/10 mL and 200 mg/40 mL. Each milliliter contains 5 mg of ipilimumab and the following inactive ingredients: mannitol 10 mg ,sodium chloride 5.85 mg , tris hydrochloride 3.15 mg, polysorbate 80 0.1 mg, diethylene triamine pentaacetic acid (DTPA) 0.04 mg, sodium hydroxide, hydrochloric acid and Water for Injection, USP at a pH of 7.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of ipilimumab was studied in 785 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg once every 3 weeks for 4 doses.

The PK of ipilimumab is linear in the dose range of 0.3 to 10 mg/kg. Following administration of YERVOY every 3 weeks, the systemic accumulation was 1.5-fold or less. Steady-state concentrations of ipilimumab were reached by the third dose; the mean Cmin at steady-state was 19.4 mcg/mL at 3 mg/kg and 58.1 mcg/mL at 10 mg/kg every 3 weeks. The mean value (percent

coefficient of variation) based on population PK analysis for the terminal half-life (t1/2) was 15.4 days (34%) and for clearance (CL) was 16.8 mL/h (38%).

Specific Populations:

The effects of various covariates on the PK of ipilimumab were assessed in population PK analyses. The CL of ipilimumab increased with increasing body weight supporting the recommended body weight (mg/kg) based dosing. The following factors had no clinically important effect on the CL of ipilimumab: age (range: 23–88 years), sex, performance status, renal impairment, mild hepatic impairment, previous cancer therapy, and baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined due to limited data available in non-Caucasian ethnic groups.

Renal Impairment: The effect of renal impairment on the CL of ipilimumab was evaluated in patients with mild (GFR <90 and ≥60 mL/min/1.73 m^2; n=349), moderate (GFR <60 and ≥30 mL/min/1.73 m^2; n=82), or severe (GFR <30 and ≥15 mL/min/1.73 m^2; n=4) renal impairment compared to patients with normal renal function (GFR ≥90 mL/min/1.73 m^2; n=350) in population PK analyses. No clinically important differences in the CL of ipilimumab were found between patients with renal impairment and patients with normal renal function. *[See Use in Specific Populations (8.6).]*

Hepatic Impairment: The effect of hepatic impairment on the CL of ipilimumab was evaluated in patients with mild hepatic impairment (n=76) compared to patients with normal hepatic function (n=708) in the population PK analyses and no clinically important differences in the CL of ipilimumab were found. YERVOY has not been studied in patients with moderate or severe hepatic impairment. *[See Use in Specific Populations (8.7).]*

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of ipilimumab has not been evaluated in long-term animal studies and the genotoxic potential of ipilimumab has not been evaluated.

Fertility studies have not been performed with ipilimumab.

14 CLINICAL STUDIES

14.1 Unresectable or Metastatic Melanoma

The safety and efficacy of YERVOY were investigated in a randomized (3:1:1), double-blind, double-dummy (trial (MDX010-20, NCT00094653) that included 676 randomized patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. Of these 676 patients, 403 were randomized to receive YERVOY at 3 mg/kg in combination with an investigational peptide vaccine with incomplete Freund's adjuvant (gp100), 137 were randomized to receive YERVOY at 3 mg/kg, and 136 were randomized to receive gp100 as a single agent. The trial enrolled only patients with HLA-A2*0201 genotype; this HLA genotype facilitates the immune presentation of

the investigational peptide vaccine. The trial excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation. YERVOY/placebo was administered at 3 mg/kg as an intravenous infusion every 3 weeks for 4 doses. Gp100/placebo was administered at a dose of 2 mg peptide by deep subcutaneous injection every 3 weeks for 4 doses. Assessment of tumor response was conducted at weeks 12 and 24, and every 3 months thereafter. Patients with evidence of objective tumor response at 12 or 24 weeks had assessment for confirmation of durability of response at 16 or 28 weeks, respectively.

The major efficacy outcome measure was overall survival (OS) in the YERVOY plus gp100 arm compared to that in the single agent gp100 arm. Secondary efficacy outcome measures were OS in the YERVOY plus gp100 arm compared to the YERVOY arm, OS in the YERVOY arm compared to the gp100 arm, best overall response rate (BORR) at week 24 between each of the trial arms, and duration of response.

Of the randomized patients, 61%, 59%, and 54% in the YERVOY plus gp100, YERVOY, and gp100 arms, respectively, were men. Twenty-nine percent were ≥65 years of age, the median age was 57 years, 71% had M1c stage, 12% had a history of previously treated brain metastasis, 98% had ECOG performance status of 0 and 1, 23% had received aldesleukin, and 38% had elevated LDH level. Sixty-one percent of patients randomized to either YERVOY-containing arm received all 4 planned doses. The median duration of follow-up was 8.9 months.

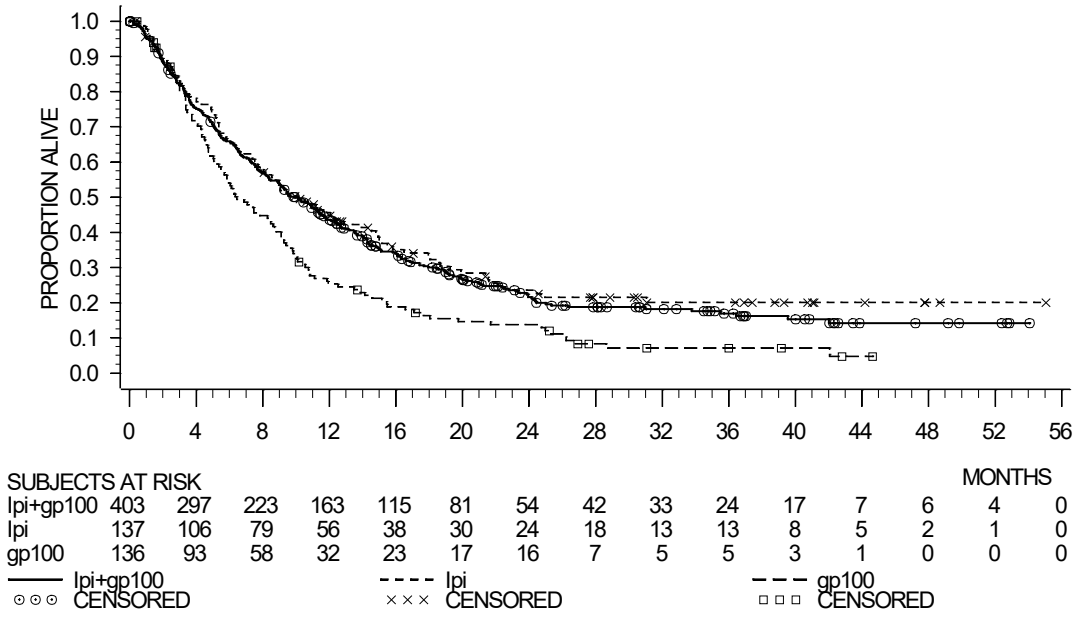
The OS results are shown in Table 4 and Figure 1.

Table 4: Overall Survival Results

	YERVOY n=137	YERVOY+gp100 n=403	gp100 n=136
Hazard Ratio (vs. gp100) (95% CI)	0.66 (0.51, 0.87)	0.68 (0.55, 0.85)	
p-value	p=0.0026[a]	p=0.0004	
Hazard Ratio (vs. YERVOY) (95% CI)		1.04 (0.83, 1.30)	
Median (months) (95% CI)	10 (8.0, 13.8)	10 (8.5, 11.5)	6 (5.5, 8.7)

[a] Not adjusted for multiple comparisons.

Figure 1: Overall Survival



The best overall response rate (BORR) as assessed by the investigator was 5.7% (95% CI: 3.7%, 8.4%) in the YERVOY plus gp100 arm, 10.9% (95% CI: 6.3%, 17.4%) in the YERVOY arm, and 1.5% (95% CI: 0.2%, 5.2%) in the gp100 arm. The median duration of response was 11.5 months in the YERVOY plus gp100 arm and has not been reached in the YERVOY or gp100 arm.

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 . Protect YERVOY 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.

MANUFACTURER

BRISTOL-MYERS SQUIBB S.r.l.
Contrada Fontana del Ceraso, Anagni, Fosinone, 03012, Italy.

LICENSE HOLDER

Bristol-Myers Squibb Israel Ltd.18 Aharon Bart St., PO BOX 3361, Kiryat Arye, Petah Tikva 4951448

REGISTRATION NUMBER

Yervoy – 147-62-33522-00