Bristol Myers Squibb

YERVOY®
(ipilimumab)

YERVOY Injection Concentrate 5mg/ml

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

YERVOY can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. 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 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 unresectable or metastatic melanoma.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of YERVOY is 3 mg/kg administered intravenously over 30-90 minutes every 3 weeks for a total of 4 doses.

Liver function tests (LFTs) and thyroid function tests should be evaluated at baseline and before each dose of YERVOY. In addition, any signs or symptoms of immune-related adverse reactions, including diarrhoea and colitis, must be assessed during treatment with YERVOY.

2.2 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:
  - Persistent moderate adverse reactions or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.
  - Failure to complete full treatment course within 16 weeks from administration of first dose.
  - Severe or life-threatening adverse reactions, including any of the following:
    - Colitis with abdominal pain, fever, ileus, or 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

2.3 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) or at room temperature (20°C to 25°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 30-90 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.

3 DOSAGE FORMS AND STRENGTHS

50 mg/10 mL (5 mg/mL)

4 CONTRAINDICATIONS

YERVOY is contraindicated in patients who are hypersensitive to ipilimumab or to any ingredient in the formulation. *[See Description (10).]*

5 WARNINGS AND PRECAUTIONS

YERVOY can result in severe and fatal immune-mediated reactions due to T-cell activation and proliferation. *[See Boxed Warning.]*

5.1 Immune-mediated Enterocolitis

In Study MDX010-20, severe, life-threatening, or fatal immune-mediated enterocolitis (diarrhea of 7 or more stools above baseline, fever, ileus, peritoneal signs; Grade 3–5) occurred in 34 (7%) YERVOY-treated patients, and moderate enterocolitis (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) occurred in 28 (5%) YERVOY-

treated patients. Across all YERVOY-treated patients (n=511), 5 (1%) patients developed intestinal perforation, 4 (0.8%) patients died as a result of complications, and 26 (5%) patients were hospitalized for severe enterocolitis.

The median time to onset was 7.4 weeks (range: 1.6–13.4) and 6.3 weeks (range: 0.3–18.9) after the initiation of YERVOY for patients with Grade 3–5 enterocolitis and with Grade 2 enterocolitis, respectively.

Twenty-nine patients (85%) with Grade 3–5 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 2.3 weeks (ranging up to 13.9 weeks) 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 5.1 weeks, and 25% were treated with high-dose corticosteroids for a median duration of 10 days prior to corticosteroid taper. Infliximab was administered to 5 of the 62 patients (8%) with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids.

Of the 34 patients with Grade 3–5 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.

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). Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-related colitis. Stool infections work-up (including CMV, other viral etiology, culture, Clostridium difficile, ova, and parasite) should be performed upon presentation of diarrhea or colitis to exclude infectious or other alternate etiologies. 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. Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered in corticosteroid-refractory immune-related colitis if other causes are excluded (including CMV infection/reactivation evaluated with viral PCR on biopsy, and other viral, bacterial, and parasitic etiology).

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).]*

5.2 Immune-mediated Hepatitis

In Study 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 3–5) occurred in 8 (2%) YERVOY-treated patients, with fatal hepatic failure in 0.2% and hospitalization in 0.4% of YERVOY-treated patients. An additional 13 (2.5%) patients 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.

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 3–5 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).]*

Concurrent administration with vemurafenib

In a Phase 1 trial, asymptomatic Grade 3 LFT elevations (ALT/AST with or without total bilirubin) were reported in 6 of 10 patients treated with the combination of YERVOY (3mg/kg) and vemurafenib (960mg or 720 mg twice daily) administered concurrently. Based on these preliminary data, the concurrent administration of YERVOY and vemurafenib is not recommended outside of a clinical trial. These results do not impact the currently approved use of YERVOY as monotherapy *[See Clinical Studies (14).]*

5.3 Immune-mediated Dermatitis

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

The median time to onset of moderate, severe, or life-threatening immune-mediated dermatitis was 3.1 weeks and ranged up to 17.3 weeks from the initiation of YERVOY.

Seven (54%) YERVOY-treated patients with severe dermatitis received high-dose corticosteroids (median dose 60 mg prednisone/day or equivalent) for up to 14.9 weeks followed by corticosteroid taper. Of these 7 patients, 6 had complete resolution; time to resolution ranged up to 15.6 weeks.

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 2.1 weeks, 7 (11%) were treated with only topical corticosteroids, and 31 (49%) did not receive systemic or topical corticosteroids. Forty-four (70%) patients with moderate dermatitis were reported to have complete resolution, 7 (11%) improved to mild (Grade 1) severity, and 12 (19%) had no reported improvement.

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.

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.

In a Phase 2 trial, the sequential treatment with vemurafenib followed by 10mg/kg ipilimumab in patients with BRAF-mutated metastatic melanoma showed a higher incidence of Grade 3+ skin adverse reactions than with ipilimumab alone. Caution should be used when ipilimumab is administered following prior vemurafenib.

5.4 Immune-mediated Neuropathies

In Study 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.

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).]*

5.5 Immune-mediated Endocrinopathies

In Study MDX010-20, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3–4) occurred in 9 (1.8%) YERVOY-treated patients. 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 (2.3%) patients 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 11 weeks and ranged up to 19.3 weeks 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).

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 thyroid function tests and clinical chemistries 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. 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).]*

Diabetes mellitus and diabetic ketoacidosis have been observed with YERVOY in combination with nivolumab. Monitor patients for hyperglycemia at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation. For symptomatic diabetes, YERVOY in combination with nivolumab should be withheld, and insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised. YERVOY in combination with nivolumab must be permanently discontinued for life-threatening diabetes. Please refer to the product insert for nivolumab for additional information.

5.6 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 MDX010-20: 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. Cases of Vogt-Koyanagi-Harada syndrome and serous retinal detachment have been reported post-marketing. Fatal or serious graft-versus-host disease (GVHD) can occur in patients who receive a CTLA-4 receptor blocking antibody either before or after allogeneic hematopoietic stem cell transplantation (HSCT). Follow patients closely for evidence of GVHD and intervene promptly. Consider the benefit versus risks of treatment with a CTLA-4 receptor blocking antibody after allogeneic HSCT.

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.

Administer corticosteroid eye drops to patients who develop uveitis, iritis, serous retinal detachment or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy. *[See Dosage and Administration (2.2).]* Transient vision loss has been reported in patients with ipilimumab-related ocular inflammations.

Solid organ transplant rejection has been reported in the post-marketing setting in patients who receive treatment with a CTLA-4 receptor blocking antibody. Treatment with ipilimumab may increase the risk of rejection in solid organ transplant recipients *[see Postmarketing experience (6.2)]*.

5.7 Infusion reaction

There were isolated reports of severe infusion reactions in clinical trials. In case of a severe infusion reaction, ipilimumab infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive ipilimumab with close monitoring. Premedication with antipyretic and antihistamine may be considered.

5.8 Patients with autoimmune disease

Patients with a history of autoimmune disease (other than vitiligo and adequately controlled endocrine deficiencies such as hypothyroidism), including those who require systemic

immunosuppressive therapy for pre-existing active autoimmune disease or for organ transplantation graft maintenance, were not evaluated in clinical trials. Ipilimumab is a T-cell potentiator that enables the immune response *[see Mechanism of action (11.1)]* and may interfere with immunosuppressive therapy, resulting in an exacerbation of the underlying disease or increased risk of graft rejection. YERVOY should be avoided in patients with severe active autoimmune disease where further immune activation is potentially imminently life threatening. YERVOY should be used with caution in other patients with a history of autoimmune disease after careful consideration of the potential risk-benefit on an individual basis.

6 ADVERSE REACTIONS

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

- Immune-mediated enterocolitis *[see Warnings and Precautions (5.1)]*.
- Immune-mediated hepatitis *[see Warnings and Precautions (5.2)]*.
- Immune-mediated dermatitis *[see Warnings and Precautions (5.3)]*.
- Immune-mediated neuropathies *[see Warnings and Precautions (5.4)]*.
- Immune-mediated endocrinopathies *[see Warnings and Precautions (5.5)]*.
- Other immune-mediated adverse reactions, including ocular manifestations *[see Warnings and Precautions (5.6)]*.

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 clinical development program excluded patients with ocular melanoma, primary CNS melanoma, active brain metastases, human immunodeficiency virus (HIV), hepatitis B, hepatitis C, active autoimmune disease, or those receiving systemic immunosuppression for organ transplantation. Exposure to YERVOY 3 mg/kg for 4 doses given by intravenous infusion in previously treated patients with unresectable or metastatic melanoma was assessed in a randomized, double-blind clinical study (Study MDX010-20). *[See Clinical Studies (13).]* One hundred thirty-one patients (median age 57 years, 60% male) received YERVOY as a single agent, 380 patients (median age 56 years, 61% male) received YERVOY with an investigational gp100 peptide vaccine (gp100), and 132 patients (median age 57 years, 54% male) received gp100 peptide vaccine alone. Patients in the study received a median of 4 doses (range: 1–4 doses). YERVOY was discontinued for adverse reactions in 10% of patients.
The most common adverse reactions (≥5%) in patients who received YERVOY at 3 mg/kg were fatigue, diarrhea, pruritus, rash, and colitis.

Table 1 presents selected adverse reactions from Study MDX010-020, 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 3–5 events.

Table 1: 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 3–5	Any Grade	Grade 3–5	Any Grade	Grade 3–5
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
General Disorders and Administration Site Conditions						
Fatigue	41	7	34	5	31	3

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

Table 2 presents the per-patient incidence of severe, life-threatening, or fatal immune-mediated adverse reactions from Study MDX010-20.

Table 2: 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.

Based on the experience in the entire clinical program for melanoma, the incidence and severity of enterocolitis and hepatitis appear to be dose dependent.

Across clinical trials, adverse reactions reported in patients treated with YERVOY 3mg/kg are presented in Table 3.

These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Rates of immune-related adverse reactions in HLA-A2*0201-positive patients who received YERVOY in MDX010-20 were similar to those observed in the overall clinical program.

The safety profile of YERVOY 3mg/kg in chemotherapy-naïve patients pooled across Phase 2 and 3 clinical trials (N=75; treated) and in treatment-naïve patients in a retrospective observational study (N=120) was similar to that in previously-treated advanced melanoma.

Table 3: Adverse reactions in patients with advanced melanoma treated with YERVOY 3 mg/kg[a]	
Infections and infestations	
Uncommon	sepsis[b], septic shock[b], urinary tract infection, respiratory tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common	tumour pain
Uncommon	paraneoplastic syndrome
Blood and lymphatic system disorders	
Common	anaemia, lymphopenia
Uncommon	haemolytic anaemia[c], thrombocytopenia, eosinophilia, neutropenia
Immune system disorders	
Uncommon	hypersensitivity, infusion related reaction
Very rare	anaphylactic reaction
Endocrine disorders	
Common	hypopituitarism (including hypophysitis)[c], hypothyroidism[c]
Uncommon	adrenal insufficiency[c], hyperthyroidism[c], hypogonadism
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	dehydration, hypokalemia
Uncommon	hyponatremia, alkalosis, hypophosphatemia, tumour lysis syndrome
Psychiatric disorders	
Common	confusional state
Uncommon	mental status changes, depression, decreased libido
Nervous system disorders	
Common	peripheral sensory neuropathy, dizziness, headache, lethargy
Uncommon	Guillain-Barré syndrome[b,c], meningitis (aseptic), syncope, cranial neuropathy, brain oedema, peripheral neuropathy, ataxia, tremor, myoclonus, dysarthria
Eye disorders	
Common	blurred vision, eye pain
Uncommon	uveitis[c], vitreous haemorrhage, iritis[c], reduced visual acuity, foreign body sensation in eyes, conjunctivitis
Very rare	Vogt-Koyanagi-Harada syndrome
Cardiac disorders	
Uncommon	arrhythmia, atrial fibrillation
Vascular disorders	
Common	hypotension, flushing, hot flush
Uncommon	vasculitis, angiopathy[b], peripheral ischaemia, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	
Common	dyspnea, cough
Uncommon	respiratory failure, acute respiratory distress syndrome[b], lung infiltration, pulmonary oedema, pneumonitis, allergic rhinitis
Gastrointestinal disorders	
Very common	diarrhoea[c], vomiting, nausea
Common	gastrointestinal haemorrhage, colitis[b,c], constipation, gastroesophageal reflux disease, abdominal pain
Uncommon	gastrointestinal perforation[b,c], large intestine perforation[b,c], intestinal perforation[b,c],

	peritonitis[b](infectious), gastroenteritis, diverticulitis, pancreatitis (autoimmune), enterocolitis, gastric ulcer, large intestinal ulcer, oesophagitis, ileus, mucosal inflammation, stomatitis
Hepatobiliary disorders	
Common	abnormal hepatic function
Uncommon	hepatic failure[b,c], hepatitis, hepatomegaly, jaundice
Skin and subcutaneous tissue disorders	
Very common	rash[c], pruritus[c]
Common	dermatitis, erythema, vitiligo, urticaria, alopecia, night sweats, dry skin
Uncommon	toxic epidermal necrolysis(including Stevens-Johnson syndrome)[b,c,d], leukocytoclastic vasculitis, skin exfoliation, eczema, hair colour changes
Musculoskeletal and connective tissue disorders	
Common	arthralgia, myalgia, musculoskeletal pain[e], muscle spasms
Uncommon	polymyalgia rheumatica, arthritis
Renal and urinary disorders	
Uncommon	renal failure[b], glomerulonephritis[c], renal tubular acidosis
Reproductive system and breast disorders	
Uncommon	amenorrhea
General disorders and administration site conditions	
Very common	fatigue, injection site reaction, pyrexia
Common	chills, asthenia, oedema, pain, influenza-like illness (symptoms)
Uncommon	multi-organ failure[b,c]
Rare	systemic inflammatory response syndrome
Investigations	
Common	increased ALT[c], increased AST[c], increased blood bilirubin, increase blood alkaline phosphatase, weight decreased
Uncommon	increase gamma-glutamyltransferase, increased blood creatinine, increased blood thyroid stimulating hormone, decreased blood cortisol, decreased blood corticotrophin, increased lipase[c], increased blood amylase[c], decreased blood testosterone
Rare	abnormal blood prolactin

a Frequencies are based on pooled data from clinical trials and expanded excess studies investigating the YERVOY 3 mg/kg dose in melanoma.

b Including fatal outcome.

c Additional information about these potentially inflammatory adverse reactions is provided in "WARNINGS AND PRECAUTIONS FOR USE. Data presented in those sections primarily reflect experience from a Phase 3 study, MDX010-20.

d Patient develops Stevens-Johnson syndrome which evolved into toxic epidermal necrolysis.

e Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.

Additional adverse reactions not listed in Table 3 have been reported in patients who received other doses (either < or > 3 mg/kg) of YERVOY in clinical trials of melanoma. These additional reactions occurred at a frequency of < 1%: meningism, myocarditis, pericardial effusion (pericarditis), cardiomyopathy, autoimmune hepatitis, erythema multiforme, autoimmune nephritis, autoimmune thyroiditis, hyperpituitarism, secondary adrenocortical insufficiency,

hypoparathyroidism, thyroiditis, episcleritis, blepharitis, eye oedema, scleritis, temporal arteritis, Raynaud's phenomenon, proctitis, palmar-plantar erythrodysaesthesia syndrome, psoriasis, hematuria, proteinuria, decreased blood thyroid stimulating hormone, decreased blood gonadotrophin, decreased thyroxine, leukopenia, polycythaemia, myasthenia gravis-like symptoms, cytokine release syndrome, sarcoidosis, neurosensory hypoacusis, autoimmune central neuropathy (encephalitis), myositis, polymyositis, and ocular myositis.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been very rarely reported with YERVOY in post-marketing use.

6.2 Postmarketing Experience

The following events have been identified during post-approval use of ipilimumab. Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made.

Blood and lymphatic system disorders: histiocytosis haematophagic, aplastic anaemia

Immune system disorders: graft-versus-host disease, solid organ transplant rejection

Gastrointestinal disorders: pancreatic exocrine insufficiency

6.3 Immunogenicity

In clinical studies, 1.1% of 1024 evaluable patients tested positive for binding antibodies against ipilimumab in an electrochemiluminescent (ECL) based assay. This assay has substantial limitations in detecting anti-ipilimumab antibodies in the presence of ipilimumab. Infusion-related or peri-infusional reactions consistent with hypersensitivity or anaphylaxis were not reported in these 11 patients nor were neutralizing antibodies against ipilimumab detected.

Because trough levels of ipilimumab interfere with the ECL assay results, a subset analysis was performed in the dose cohort with the lowest trough levels. In this analysis, 6.9% of 58 evaluable patients, who were treated with 0.3 mg/kg dose, tested positive for binding antibodies against ipilimumab.

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 YERVOY with the incidences of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

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

The use of systemic corticosteroids at baseline, before starting YERVOY, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of

YERVOY. However, systemic corticosteroids or other immunosuppressants can be used after starting YERVOY to treat immune-related adverse reactions. The use of systemic corticosteroids after starting YERVOY treatment does not appear to impair the efficacy of YERVOY.

The use of anticoagulants is known to increase the risk of gastrointestinal hemorrhage. Since gastrointestinal hemorrhage is an adverse reaction with YERVOY *[see ADVERSE REACTIONS (6)]*, patients who require concomitant anticoagulant therapy should be monitored closely.

8 USE IN SPECIFIC POPULATIONS

8.1 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 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 (12.2).]*

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.

8.3 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.

8.4 Pediatric Use

Safety and effectiveness of YERVOY have not been established in pediatric patients below 18 years of age.

8.5 Geriatric Use

Of the 511 patients treated with YERVOY at 3 mg/kg, 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 (11.2).]*

8.7 Hepatic Impairment

No dose adjustment is needed for patients with mild hepatic impairment (total bilirubin [TB] >1.0 × to 1.5 × the upper limit of normal [ULN] or AST >ULN). YERVOY has not been studied in patients with moderate (TB >1.5 × to 3.0 × ULN and any AST) or severe (TB >3 × ULN and any AST) hepatic impairment. *[See Clinical Pharmacology (11.2).]*

9 OVERDOSAGE

There is no information on overdosage with YERVOY.

10 DESCRIPTION

YERVOY (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. Each milliliter contains 5 mg of ipilimumab and the following inactive ingredients: diethylene triamine pentaacetic acid (DTPA) (0.04 mg), mannitol (10 mg), polysorbate 80 (vegetable origin) (0.1 mg), sodium chloride (5.85 mg), tris hydrochloride (3.15 mg), sodium hydroxide (for pH-adjustment), hydrochloric acid (for pH-adjustment) and Water for Injection, USP at a pH of 7.

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

CTLA-4 is a negative regulator of T-cell activation. Ipilimumab 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. The mechanism of action of ipilimumab's effect in patients with melanoma is indirect, possibly through T-cell mediated anti-tumor immune responses.

11.2 Pharmacokinetics

The pharmacokinetics of ipilimumab were 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. Peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve (AUC) of ipilimumab increased dose proportionally within the dose range examined. Upon repeated dosing every 3 weeks, the clearance (CL) of ipilimumab was found to be time-invariant, and systemic accumulation was 1.5-fold or less. Steady-state concentrations of ipilimumab were reached by the third dose; the mean C_{min} at steady-state was 19.4 mcg/mL following repeated doses of 3 mg/kg. The mean value (% coefficient of variation) generated through population pharmacokinetic analysis for the terminal half-life ($t_{1/2}$) was 15.4 days (34%) and for CL was 16.8 mL/h (38%).

Specific Populations: The effects of various covariates on the pharmacokinetics of ipilimumab were assessed in population pharmacokinetic analyses. The CL of ipilimumab increased with increasing body weight; however, no dose adjustment is recommended for body weight after administration on a mg/kg basis. The following factors had no clinically important effect on the CL of ipilimumab: age (range: 23–88 years), gender, 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 pharmacokinetic 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 (TB 1.0 × to 1.5 × ULN or AST >ULN as defined using the National Cancer Institute criteria of hepatic dysfunction; n=76) compared to patients with normal hepatic function (TB and AST ≤ULN; n=708) in the population pharmacokinetic analyses. No clinically important differences in the CL of ipilimumab were found between patients with mild hepatic impairment and normal hepatic function. YERVOY has not been studied in patients with moderate (TB >1.5 × to 3 × ULN and any AST) or severe hepatic impairment (TB >3 × ULN and any AST). *[See Use in Specific Populations (8.7).]*

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

The genotoxic potential of ipilimumab has not been evaluated.

Impairment of Fertility

Fertility studies have not been performed with ipilimumab.

12.2 Animal Toxicology and/or Pharmacology

In addition to the severe findings of abortion, stillbirths, and postnatal deaths observed in pregnant cynomolgus monkeys that received ipilimumab every 3 weeks from the onset of organogenesis in the first trimester through parturition *[see Use in Specific Populations (8.1)]*, 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 clinically recommended 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 3–4 weeks of age with massive lymphoproliferation and multiorgan tissue destruction.

13 CLINICAL STUDIES

The safety and efficacy of YERVOY were investigated in a randomized (3:1:1), double-blind, double-dummy study (Study 1) 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 alone. The study enrolled only patients with HLA-A2*0201 genotype; this HLA genotype facilitates the immune presentation of the investigational peptide vaccine. The study 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+gp100 arm compared to that in the gp100 arm. Secondary efficacy outcome measures were OS in the YERVOY+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 study arms, and duration of response.

Of the randomized patients, 61%, 59%, and 54% in the YERVOY+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.

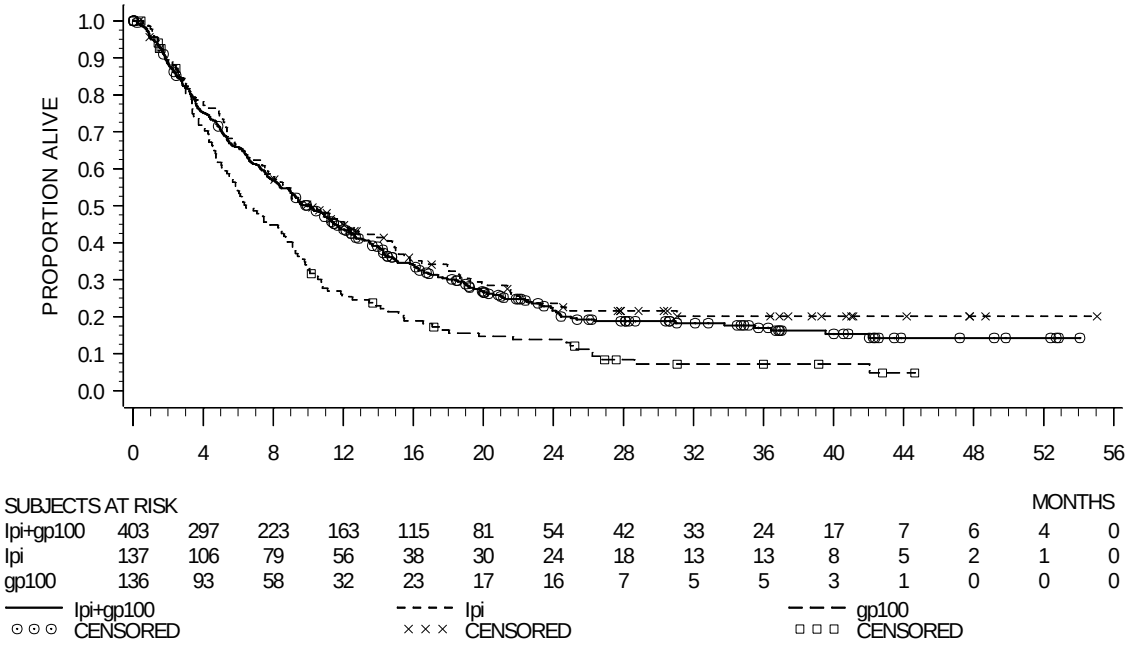
The OS results are shown in Table 4 and Figure 1.

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+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+gp100 arm and has not been reached in the YERVOY or gp100 arm.

Concurrent Administration with Vemurafenib: A Phase 1 study was conducted to investigate the safety of the concurrent administration of vemurafenib and YERVOY in patients with $BRAF^{V600}$-mutated metastatic melanoma not previously treated with CTLA-4–blocking antibodies or with BRAF or MEK inhibitors. Following a 1-month lead-in with monotherapy vemurafenib (960 mg or 720 mg twice daily), patients received combination therapy with YERVOY (3 mg/kg intravenously every 3 weeks) and vemurafenib administered concurrently. Of the 10 patients who received the combination regimen, 6 developed Grade 3 elevation of ALT/AST, 1 of which also developed Grade 3 elevation of total bilirubin. All were asymptomatic and reversible with either interruption or permanent discontinuation of the drugs and/or treatment with corticosteroids. *[See Warnings and Precautions (5.2).]*

14 HOW SUPPLIED/STORAGE AND HANDLING

YERVOY is available as follows:

Carton Contents
• One 50 mg vial (5 mg/mL), single-use vial (10mL)

Store YERVOY under refrigeration at 2°C to 8°C. Do not freeze. Protect vials from light. Since YERVOY does not contain preservatives, any unused portion remaining in the vial must be discarded.

Product Registrant:

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