HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use YERVOY safely and effectively. See full prescribing information for YERVOY.

YERVOY® (ipilimumab) injection, for intravenous use
Initial U.S. Approval: 2011

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS
See full prescribing information for complete boxed warning.

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. (2.3)

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. (5.1, 5.2, 5.3, 5.4, 5.5)

----------INDICATIONS AND USAGE----------

YERVOY is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody indicated for:

- Treatment of unresectable or metastatic melanoma in adults and pediatric patients (12 years and older). (1.1)
- Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy. (1.2)

----------DOSAGE AND ADMINISTRATION----------

- Unresectable or metastatic melanoma:
  - 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of 4 doses. (2.1)
- Adjuvant melanoma:
  - 10 mg/kg administered intravenously over 90 minutes every 3 weeks for 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years or until documented disease recurrence or unacceptable toxicity. (2.2)
- Permanently discontinue for severe adverse reactions. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 50 mg/10 mL (5 mg/mL) (3)
- Injection: 200 mg/40 mL (5 mg/mL) (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

Immune-mediated adverse reactions: Permanently discontinue for severe reactions. Withhold dose for moderate immune-mediated adverse reactions until return to baseline, improvement to mild severity, or complete resolution, and patient is receiving less than 7.5 mg prednisone or equivalent per day. Administer systemic high-dose corticosteroids for severe, persistent, or recurring immune-mediated reactions. (5.1, 5.2, 5.3, 5.4, 5.5)

- Immune-mediated hepatitis: Evaluate liver function tests before each dose of YERVOY. (5.2)
- Immune-mediated endocrinopathies: Monitor clinical chemistries, ACTH level, and thyroid function tests prior to each dose. Evaluate at each visit for signs and symptoms of endocrinopathy. Institute hormone replacement therapy as needed. (5.5)
- Embryo-fetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.7)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥5%) are fatigue, diarrhea, pruritus, rash, and colitis. Additional common adverse reactions at the 10 mg/kg dose (≥5%) include nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Discontinue nursing during treatment with YERVOY. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2017

FULL PRESCRIBING INFORMATION: CONTENTS *

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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 (2.3)]*.

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

1.1 Unresectable or Metastatic Melanoma

YERVOY is indicated for the treatment of unresectable or metastatic melanoma in adults and pediatric patients (12 years and older) *[see Clinical Studies (14.1)]*.

1.2 Adjuvant Treatment of Melanoma

YERVOY is indicated for the adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing for Unresectable or Metastatic Melanoma

The recommended dose of YERVOY 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 (14.1)]*.

2.2 Recommended Dosing for Adjuvant Treatment of Melanoma

The recommended dose of YERVOY is 10 mg/kg administered intravenously over 90 minutes every 3 weeks for 4 doses followed by 10 mg/kg every 12 weeks for up to 3 years *[see Clinical Studies (14.2)]*. In the event of toxicity, doses are omitted, not delayed.

2.3 Recommended Dose Modifications

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 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 v3)	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

2.4 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, 36°F to 46°F) or at room temperature (20°C to 25°C, 68°F to 77°F).
- 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

None.

5 WARNINGS AND PRECAUTIONS

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

5.1 Immune-Mediated Enterocolitis

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 (2.3)]*.

Metastatic Melanoma

In patients receiving YERVOY 3 mg/kg in Trial 1, 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.

Adjuvant Treatment of Melanoma

In patients receiving YERVOY 10 mg/kg in Trial 2, Grade 3 to 5 immune-mediated enterocolitis occurred in 76 patients (16%) and Grade 2 enterocolitis occurred in 68 patients (14%). Seven patients (1.5%) developed intestinal perforation and 3 patients (0.6%) died as a result of complications *[see Adverse Reactions (6.1)]*.

The median time to onset for Grade 3 to 4 enterocolitis was 1.1 months (range: 1 day to 33.1 months) and for Grade 2 enterocolitis was 1.1 months (range: 1 day to 20.6 months).

Seventy-one patients (95%) with Grade 3 to 4 enterocolitis were treated with systemic corticosteroids. The median duration of treatment was 4.7 months (ranging up to 52.3 months).

Of the 68 patients with moderate enterocolitis, 51 patients (75%) were treated with systemic corticosteroids with a median duration of treatment of 3.5 months (ranging up to 52.2 months). Non-corticosteroids immunosuppression, consisting almost exclusively of infliximab, was used to treat 36% of patients with Grade 3 to 4 enterocolitis and 15% of patients with a Grade 2 event.

Of the 75 patients with Grade 3 to 4 immune-mediated enterocolitis, 86% experienced complete resolution, 3% experienced improvement to Grade 1, and 11% did not improve. Among the 68 patients with Grade 2 enterocolitis, 94% experienced complete resolution, 3% experienced improvement to Grade 1, and 3% 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 (2.3)]*.

Metastatic Melanoma

In patients receiving YERVOY 3 mg/kg in Trial 1, 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.

Adjuvant Treatment of Melanoma

In patients receiving YERVOY 10 mg/kg in Trial 2, Grade 3 to 4 immune-mediated hepatitis occurred in 51 patients (11%) and moderate Grade 2 immune-mediated hepatitis occurred in 22 patients (5%). Liver biopsy performed in 6 patients with Grade 3 to 4 hepatitis showed evidence of toxic or autoimmune hepatitis. The median time to onset for Grade 3 to 4 hepatitis was 2.0 months (range: 1 day to 4.2 months) and for Grade 2 hepatitis was 1.4 months (range: 13 days to 6.5 months). Of the 51 patients with Grade 3 to 4 immune-mediated hepatitis, 94% experienced complete resolution, 4% experienced improvement to Grade 1, and 2% did not improve. Of the

22 patients with Grade 2 immune-mediated hepatitis, 91% experienced complete resolution and 9% did not improve.

Forty-six patients (90%) with Grade 3 to 4 hepatitis were treated with systemic corticosteroids. The median duration of treatment was 4.4 months (ranging up to 56.1 months). Sixteen patients (73%) with moderate hepatitis were treated with systemic corticosteroids. The median duration of treatment was 2.6 months (ranging up to 41.4 months).

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

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 (2.3)]*.

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.

Metastatic Melanoma

In patients receiving YERVOY 3 mg/kg in Trial 1, 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 3 to 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.

Adjuvant Treatment of Melanoma

In patients receiving YERVOY 10 mg/kg in Trial 2, Grade 3 to 4 immune-mediated dermatitis occurred in 19 patients (4%). There were 99 patients (21%) with moderate (Grade 2) dermatitis. The median time to onset for Grade 3 to 4 dermatitis was 14 days (range: 5 days to 11.3 months) and for Grade 2 dermatitis was 11 days (range: 1 day to 16.6 months).

Sixteen patients (84%) with Grade 3 to 4 dermatitis were treated with systemic corticosteroids for a median of 21 days (ranging up to 49.2 months) resulting in complete resolution of dermatitis within a median time of 4.3 months (range up to 44.4 months). Of the 3 patients (16%) not treated with systemic or topical corticosteroids, 2 (11%) had complete resolution and 1 had improvement to Grade 1.

Of the 99 patients with Grade 2 dermatitis, 67 (68%) were treated with systemic corticosteroids for a median of 2.6 months, 16 (16%) were treated with only topical corticosteroids and 16 (16%) did not receive systemic or topical corticosteroids. Seventy-seven patients (78%) had complete resolution, 15 (15%) improved to mild (Grade 1) severity, and 7 (7%) did not improve.

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 (2.3)]*.

Metastatic Melanoma

In patients receiving YERVOY 3 mg/kg in Trial 1, 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.

Adjuvant Treatment of Melanoma

In patients receiving YERVOY 10 mg/kg in Trial 2, Grade 3 to 5 immune-mediated neuropathy occurred in 8 patients (2%); the sole fatality was due to complications of Guillain-Barré syndrome *[see Adverse Reactions (6.1)]*. Moderate Grade 2 immune-mediated neuropathy occurred in 1 patient (0.2%).

The time to onset across the 9 patients with Grade 2 to 5 immune-mediated neuropathy ranged from 1.4 to 27.4 months. All 8 patients with Grade 3 to 5 neuropathy were treated with systemic corticosteroids (range: 3 days to 38.3 months) and 3 also received tacrolimus. Four of the 8 patients with Grade 3 to 5 immune-mediated neuropathy experienced complete resolution, 1 improved to Grade 1, and 3 did not improve. The single patient with Grade 2 immune-mediated neuropathy experienced complete resolution without the use of corticosteroids.

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 (2.3)]*.

Metastatic Melanoma

In patients receiving YERVOY 3 mg/kg in Trial 1, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3 to 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).

Adjuvant Treatment of Melanoma

In patients receiving YERVOY 10 mg/kg in Trial 2, Grade 3 to 4 immune-mediated endocrinopathies occurred in 39 patients (8%) and Grade 2 immune-mediated endocrinopathies in 93 patients (20%). Of the 39 patients with Grade 3 to 4 immune-mediated endocrinopathies, 35 patients had hypopituitarism (associated with one or more secondary endocrinopathies, e.g., adrenal insufficiency, hypogonadism, and hypothyroidism), 3 patients had hyperthyroidism, and 1 had primary hypothyroidism. The median time to onset of Grade 3 to 4 immune-mediated endocrinopathy was 2.2 months (range: 2 days to 8 months). Twenty-seven of the 39 patients (69%) were hospitalized for immune-mediated endocrinopathies, and 4 patients (10%) were reported to have resolution.

Of the 93 patients with Grade 2 immune-mediated endocrinopathy, 74 had primary hypopituitarism (associated with one or more secondary endocrinopathy, e.g., adrenal insufficiency, hypogonadism, and hypothyroidism), 9 had primary hypothyroidism, 3 had hyperthyroidism, 3 had thyroiditis with hypo- or hyperthyroidism, 2 had hypogonadism, 1 had both hyperthyroidism and hypopituitarism, and 1 subject developed Graves' ophthalmopathy. The median time to onset of Grade 2 immune-mediated endocrinopathy was 2.1 months (range: 9 days to 19.3 months), and 20% were reported to have resolution.

One hundred twenty-four patients received systemic corticosteroids as immunosuppression and/or adrenal hormone replacement for Grade 2 to 4 immune-mediated endocrinopathy. Of these, 42 (34%) were able to discontinue corticosteroids. Seventy-three patients received thyroid

hormones for treatment of Grade 2 to 4 immune-mediated hypothyroidism. Of these, 14 patients (19%) were able to discontinue thyroid replacement therapy.

5.6 Other Immune-Mediated Adverse Reactions, Including Ocular Manifestations

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, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy *[see Dosage and Administration (2.3)]*.

Metastatic Melanoma

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

Adjuvant Treatment of Melanoma

In Trial 2, the following clinically significant immune-mediated adverse reactions were seen in less than 1% of YERVOY-treated patients unless specified: eosinophilia (2.1%), pancreatitis (1.3%), meningitis, pneumonitis, sarcoidosis, pericarditis, uveitis, and fatal myocarditis *[see Adverse Reactions (6.1)]*.

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.

5.7 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)]*.

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)]*.

In patients receiving YERVOY 3 mg/kg for unresectable or metastatic melanoma in Trial 1, 15% of patients receiving monotherapy and 12% of patients treated in combination with gp100 peptide vaccine experienced Grade 3 to 5 immune-mediated reactions. In patients receiving YERVOY 10 mg/kg for adjuvant treatment of melanoma in Trial 2, 41% 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 in Trial 1, a randomized trial in patients with unresectable or metastatic melanoma and to YERVOY 10 mg/kg in Trial 2, 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 Trials 1 and 2 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 Trial 1, 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).

Trial 1 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 Trial 1, 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 Trial 1

	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 to 5	Any Grade	Grade 3 to 5	Any Grade	Grade 3 to 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 from Trial 1.

Table 3: Severe to Fatal Immune-Mediated Adverse Reactions in Trial 1

	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.

Adjuvant Treatment of Melanoma

The safety of YERVOY was evaluated in Trial 2, a randomized (1:1), double-blind, placebo-controlled trial in which 945 patients with resected Stage IIIA (>1 mm nodal involvement), IIIB, and IIIC (with no in-transit metastases) cutaneous melanoma received YERVOY 10 mg/kg (n=471) or placebo (n=474) administered as an intravenous infusion for 4 doses every 3 weeks followed by 10 mg/kg every 12 weeks beginning at Week 24 up to a maximum of 3 years *[see Clinical Studies (14.2)]*. In this trial, 36% of patients received YERVOY for longer than 6 months and 26% of patients received YERVOY for longer than 1 year. YERVOY-treated patients in the trial received a median of 4 doses (range: 1 to 16).

Trial 2 excluded patients with prior systemic therapy for melanoma, autoimmune disease, a condition requiring systemic immunosuppression, or a positive test for hepatitis B, hepatitis C, or HIV.

The trial population characteristics were: median age 51 years (range: 18 to 84 years), 62% male, 99% white, and baseline ECOG performance status 0 (94%).

YERVOY was discontinued for adverse reactions in 52% of patients.

Table 4 presents selected adverse reactions from Trial 2 which occurred in at least 5% of YERVOY-treated patients and with at least 5% increased incidence over the placebo group for all-grade events.

Table 4: Selected Adverse Reactions in Trial 2

	Percentage (%) of Patients[a]			
	YERVOY 10 mg/kg n=471		Placebo n=474	
System Organ Class/ Preferred Term	Any Grade	Grade 3 to 5	Any Grade	Grade 3 to 5
Skin and Subcutaneous Tissue Disorders				
Rash	50	2.1	20	0
Pruritus	45	2.3	15	0
Gastrointestinal Disorders				
Diarrhea	49	10	30	2.1
Nausea	25	0.2	18	0
Colitis[b]	16	8	1.5	0.4
Vomiting	13	0.4	6	0.2
Investigations				
Weight Decreased	32	0.2	9	0.4
General Disorders and Administration-Site Conditions				
Fatigue	46	2.3	38	1.5
Pyrexia	18	1.1	4.9	0.2
Nervous System Disorders				
Headache	33	0.8	18	0.2
Metabolism and Nutrition Disorders				
Decreased Appetite	14	0.2	3.4	0.2
Psychiatric Disorders				
Insomnia	10	0	4.4	0

[a] Incidences presented in this table are based on reports of adverse events regardless of causality.
[b] Includes 1 death.

Table 5 presents selected laboratory abnormalities from Trial 2 which occurred in at least 10% of YERVOY-treated patients at a higher incidence compared to placebo.

Table 5: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of YERVOY-Treated Patients (Trial 2)[a]

	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	YERVOY		Placebo	
Test	All Grades	Grade 3 to 4	All Grades	Grade 3 to 4
Chemistry				
Increased ALT	46	10	16	0
Increased AST	38	9	14	0.2
Increased lipase[b]	26	9	17	4.5
Increased amylase[b]	17	2.0	7	0.6
Increased alkaline phosphatase	17	0.6	6	0.2
Increased bilirubin	11	1.5	9	0
Increased creatinine	10	0.2	6	0
Hematology				
Decreased hemoglobin	25	0.2	14	0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available. Excluding lipase and amylase, YERVOY group (range: 466 to 470 patients) and placebo group (range: 472 to 474 patients).

[b] For lipase and amylase, YERVOY group (range: 447 to 448 patients) and placebo group (range: 462 to 464 patients).

Table 6 presents the per-patient incidence of severe, life-threatening, or fatal immune-mediated adverse reactions from Trial 2.

Table 6: Severe to Fatal Immune-Mediated Adverse Reactions in Trial 2

	Percentage (%) of Patients
	YERVOY 10 mg/kg n=471
Any Immune-Mediated Adverse Reaction	41
Enterocolitis[a,b]	16
Hepatitis	11
Dermatitis	4.0
Neuropathy[a]	1.7
Endocrinopathy	8
Hypopituitarism	7
Primary hypothyroidism	0.2
Hyperthyroidism	0.6

Table 6: Severe to Fatal Immune-Mediated Adverse Reactions in Trial 2

	Percentage (%) of Patients
	YERVOY 10 mg/kg n=471
Other	
Myocarditis[a]	0.2
Meningitis	0.4
Pericarditis[c]	0.2
Pneumonitis	0.2
Uveitis	0.2

[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.

6.2 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)

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

Eleven (1.1%) of 1024 evaluable patients with unresectable or metastatic melanoma tested positive for treatment-emergent binding antibodies against ipilimumab (TE-ADAs) in an electrochemiluminescent (ECL) based assay. This assay had substantial limitations in detecting anti-ipilimumab antibodies in the presence of ipilimumab. Seven (4.9%) of 144 patients receiving ipilimumab and 7 (4.5%) of 156 patients receiving placebo for the adjuvant treatment of melanoma tested positive for TE-ADAs using an ECL assay with improved drug tolerance.

No patients tested positive for neutralizing antibodies. No infusion-related reactions occurred in patients who tested positive for TE-ADAs.

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

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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.

A Pregnancy Safety Surveillance Study has been established to collect information about pregnancies in women who have received YERVOY. Healthcare providers are encouraged to enroll patients or have their patients enroll directly by calling 1-844-593-7869.

Data

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 present in human milk. In monkeys, ipilimumab was present in milk *(see Data)*. There are no data to assess the effects of YERVOY on milk production. Advise women to discontinue nursing 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

The safety and effectiveness of YERVOY have been established in pediatric patients 12 years and older. Use of YERVOY in this age group is supported by evidence from adequate and well-controlled studies of YERVOY in adults and population pharmacokinetic data demonstrating that the exposure at a dose of 3 mg/kg in the pediatric and adult populations is comparable. In addition, the tumor biology and course of advanced melanoma is sufficiently similar in adults and pediatric patients 12 years and older to allow extrapolation of data from adults to pediatric patients.

The safety and effectiveness for pediatric patients less than 12 years of age has not been established *[see Dosage and Administration (2.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

YERVOY was evaluated in a total of 45 pediatric patients across two clinical trials. In a dose-finding trial, 33 pediatric patients with relapsed or refractory solid tumors were evaluated. The median age was 13 years (range 2 to 21 years), and 20 patients were ≥12 years old. YERVOY was administered at doses of 1, 3, 5, and 10 mg/kg intravenously over 90 minutes every 3 weeks for 4 doses and then every 12 weeks thereafter until progression or treatment discontinuation.

YERVOY was also evaluated in an open-label, single-arm, trial in 12 pediatric patients ≥12 years old (range 12 to 16 years) with previously treated or untreated, unresectable Stage 3 or 4 malignant melanoma. Patients received YERVOY 3 mg/kg (4 patients) or 10 mg/kg (8 patients) intravenously over 90 minutes every 3 weeks for 4 doses.

Of the 17 patients ≥12 years of age with melanoma treated with YERVOY across both studies, two patients experienced objective responses including one partial response that was sustained for 16 months. There were no responses in patients with non-melanoma solid tumors.

The overall safety profile of YERVOY in children and adolescents was consistent with the safety profile in adults.

Pediatric Pharmacokinetics (PK)

Based on a population PK analysis using available pooled data from 565 patients from 4 phase 2 adult studies (N=521) and 2 pediatric studies (N=44), body weight normalized clearance of ipilimumab is comparable between adult and pediatric patients. In pediatric patients with a dosing regimen of 3 mg/kg every 3 weeks, the model simulated geometric mean (CV%) steady-state serum peak and trough concentrations of ipilimumab were 65.8 (17.6%) and 20.7 (33.1%) mcg/mL (for 2 to 6 years old), 70.1 (19.6%) and 19.6 (42.9%) mcg/mL (for 6 to <12 years old), and 73.3 (20.6%) and 17.8 (50.8%) mcg/mL (for 12 years and older), which are comparable to those in adult patients.

8.5 Geriatric Use

Of the 511 patients treated with YERVOY in Trial 1, 28% were 65 years and over. No overall differences in safety or efficacy were reported between the elderly patients (65 years and over) and younger patients (less than 65 years).

Trial 2 did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

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

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 and 200 mg/40 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), 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 C_{min} 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 ($t_{1/2}$) 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 to 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)]*.

Pediatric Population: [see Use in Specific Populations (8.4)].

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 (Trial 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 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.

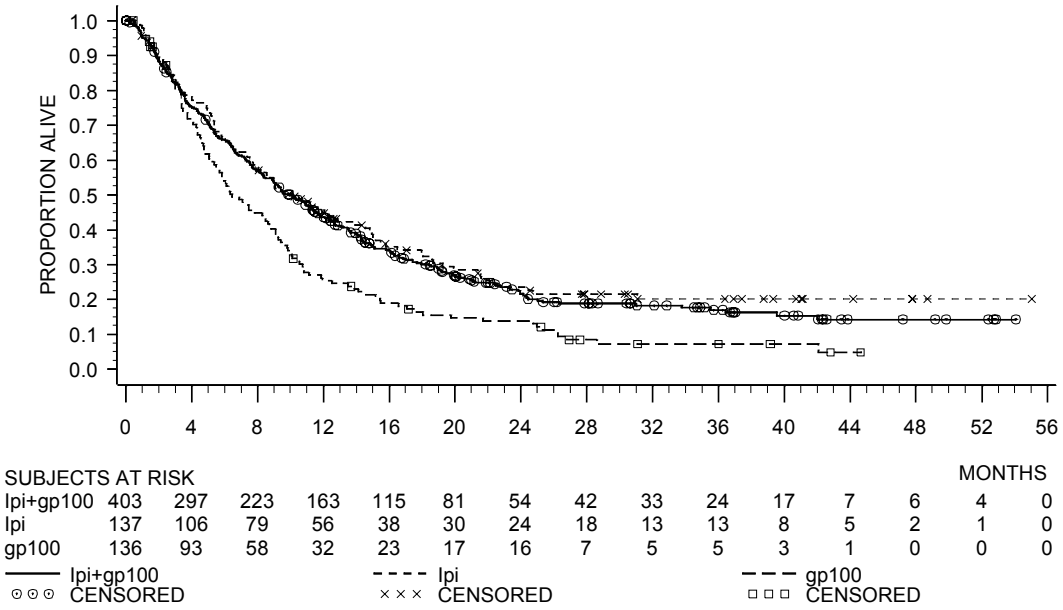
The OS results are shown in Table 7 and Figure 1.

Table 7: 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.

14.2 Adjuvant Treatment of Melanoma

The safety and efficacy of YERVOY for the adjuvant treatment of melanoma were investigated in Trial 2, a randomized (1:1), double-blind, placebo-controlled trial in patients with resected Stage IIIA (>1 mm nodal involvement), IIIB, and IIIC (with no in-transit metastases) histologically confirmed cutaneous melanoma. Patients were randomized to receive YERVOY 10 mg/kg or placebo as an intravenous infusion every 3 weeks for 4 doses, followed by YERVOY 10 mg/kg or placebo every 12 weeks from Week 24 to Week 156 (3 years) or until documented disease recurrence or unacceptable toxicity. Enrollment required complete resection of melanoma with full lymphadenectomy within 12 weeks prior to randomization. Patients with prior therapy for melanoma, autoimmune disease, and prior or concomitant use of immunosuppressive agents were ineligible. Randomization was stratified by stage according to American Joint Committee on Cancer (AJCC) 2002 classification (Stage IIIA >1 mm nodal involvement, Stage IIIB, Stage IIIC with 1 to 3 involved lymph nodes, and Stage IIIC with ≥4 involved lymph nodes) and by region (North America, Europe, and Australia). The major efficacy outcome measures were recurrence-free survival (RFS) defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurs first and assessed by an independent review committee and overall survival. Tumor assessment was conducted every 12 weeks for the first 3 years then every 24 weeks until distant recurrence.

Among 951 patients enrolled, 475 were randomized to receive YERVOY and 476 to placebo. Median age was 51 years old (range: 18 to 84), 62% were male, 99% were white, 94% had ECOG performance status of 0. With regard to disease stage, 20% had Stage IIIA with lymph nodes >1 mm, 44% had Stage IIIB, and 36% had Stage IIIC (with no in-transit metastases). Other disease characteristics of the trial population were: clinically palpable lymph nodes (58%), 2 or more positive lymph nodes (54%), and ulcerated primary lesions (42%).

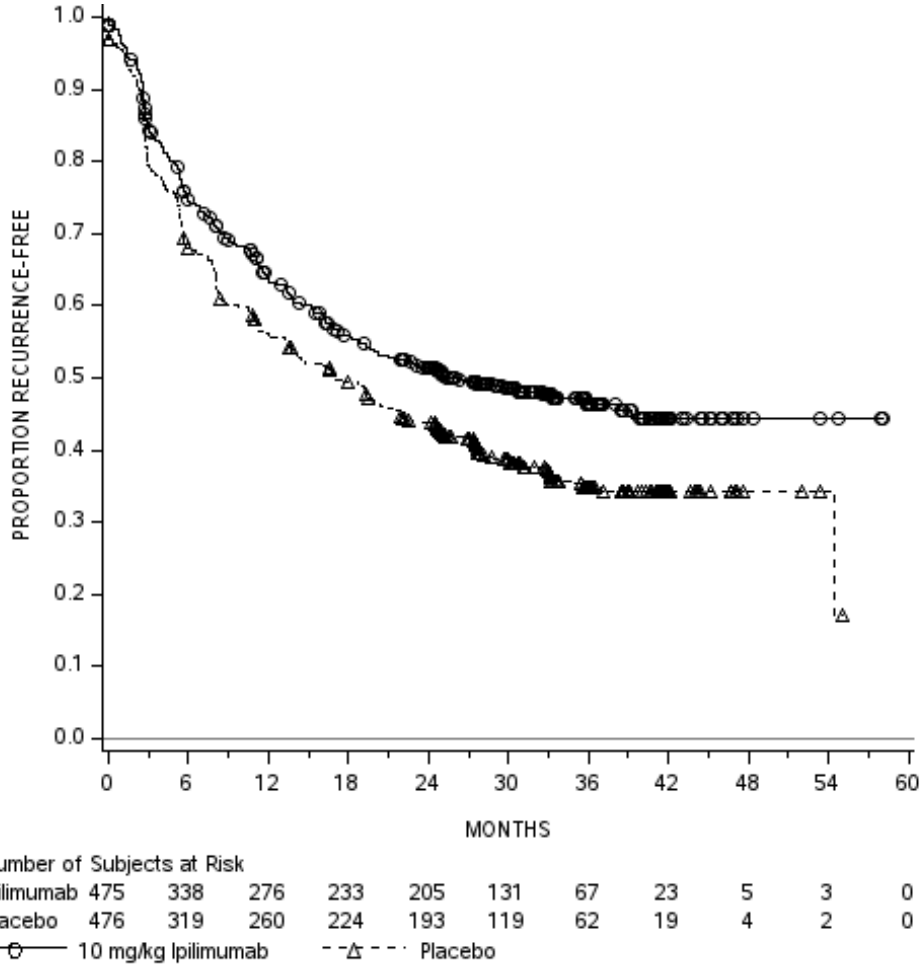
The RFS results are in Table 8 and Figure 2. Based on the observation of 282 deaths at the time of the RFS analysis, the final analysis of overall survival has not occurred (planned at the time of 491 deaths).

Table 8: Efficacy Results in Trial 2

Recurrence-Free Survival	YERVOY N=475	Placebo N=476
Number of Events, n (%)	234 (49%)	294 (62%)
Recurrence	220	289
Death	14	5
Median (months)	26	17
(95% CI)	(19, 39)	(13, 22)
Hazard Ratio	0.75	
(95% CI)	(0.64, 0.90)	
p-value (stratified log-rank[a])	p<0.002	

[a] Stratified by disease stage.

Figure 2: Recurrence-Free Survival



16 HOW SUPPLIED/STORAGE AND HANDLING

YERVOY is available as follows:

Carton Contents	NDC
One 50 mg vial (5 mg/mL), single-use vial	NDC 0003-2327-11
One 200 mg vial (5 mg/mL), single-use vial	NDC 0003-2328-22

Store YERVOY under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect vials from light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

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. Advise females who may have been exposed to YERVOY during pregnancy to contact Bristol-Myers Squibb at 1-800-721-5072 *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)]*.

Advise patients that there is a Pregnancy Safety Surveillance Study that monitors pregnancy outcomes in women exposed to YERVOY during pregnancy, and they can be enrolled by calling 1-844-593-7869 *[see Use in Specific Populations (8.1)]*.

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)]*.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
U.S. License No. 1713

[print code]

MEDICATION GUIDE
YERVOY® (yur-voi)
(ipilimumab)
injection

What is the most important information I should know about YERVOY?

YERVOY can cause serious side effects in many parts of your body which can lead to death. These problems may happen anytime during treatment with YERVOY or after you have completed treatment.

Call your healthcare provider right away if you develop any of these signs or symptoms or they get worse. Do not try to treat symptoms yourself.

Intestinal problems (colitis) that can cause tears or holes (perforation) in the intestines. Signs and symptoms of colitis may include:

- diarrhea (loose stools) or more bowel movements than usual
- blood in your stools or dark, tarry, sticky stools
- stomach pain (abdominal pain) or tenderness

Liver problems (hepatitis) that can lead to liver failure. Signs and symptoms of hepatitis may include:

- yellowing of your skin or the whites of your eyes
- dark urine (tea colored)
- nausea or vomiting
- pain on the right side of your stomach
- bleeding or bruise more easily than normal

Skin problems that can lead to severe skin reaction. Signs and symptoms of severe skin reactions may include:

- skin rash with or without itching
- sores in your mouth
- your skin blisters or peels

Nerve problems that can lead to paralysis. Symptoms of nerve problems may include:

- unusual weakness of legs, arms, or face
- numbness or tingling in hands or feet

Hormone gland problems (especially the pituitary, adrenal, and thyroid glands). Signs and symptoms that your glands are not working properly may include:

- persistent or unusual headaches
- unusual sluggishness
- feeling cold all the time
- weight gain
- changes in mood or behavior such as decreased sex drive, irritability, or forgetfulness
- dizziness or fainting

Eye problems. Symptoms may include:

- blurry vision, double vision, or other vision problems
- eye pain or redness

Getting medical treatment right away may keep the problem from becoming more serious.

Your healthcare provider will check you for these problems during treatment with YERVOY. Your healthcare provider may treat you with corticosteroid medicines. Your healthcare provider may need to delay or completely stop treatment with YERVOY if you have severe side effects.

What is YERVOY?

YERVOY is a prescription medicine used to treat a kind of skin cancer called melanoma. YERVOY may be used:

- in adults and children 12 years and older when melanoma has spread or cannot be removed by surgery
- to help prevent melanoma from coming back after it and lymph nodes that contain cancer have been removed by surgery

It is not known if YERVOY is safe and effective in children less than 12 years of age.

Before you receive YERVOY, tell your healthcare provider about all your medical conditions, including if you:

- have immune system problems (autoimmune disease), such as ulcerative colitis, Crohn's disease, lupus, or sarcoidosis
- have had an organ transplant
- have liver problems
- are pregnant or plan to become pregnant. YERVOY can harm your unborn baby.
  - Females who are able to become pregnant should use effective birth control during treatment with YERVOY and for 3 months after the last dose of YERVOY.
  - If you become pregnant or think you are pregnant, tell your healthcare provider right away. You or your healthcare provider should contact Bristol-Myers Squibb at 1-800-721-5072 as soon as you become aware of the pregnancy.
  - **Pregnancy Safety Surveillance Study: Females** who become pregnant during treatment with YERVOY are encouraged to enroll in a Pregnancy Safety Surveillance Study. The purpose of this study is to collect information about the health of you and your baby. You or your healthcare provider can enroll you in the Pregnancy Safety Surveillance Study by calling 1-844-593-7869.
- are breastfeeding or plan to breastfeed. It is not known if YERVOY passes into your breast milk.
  - **Do not** breastfeed during treatment with YERVOY and for 3 months after the last dose of YERVOY.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive YERVOY?

- YERVOY is given to you into your vein through an intravenous (IV) line over 90 minutes.
- Your healthcare provider will decide how many treatments you will need.
- Your healthcare provider will do blood tests before starting and during treatment with YERVOY.
- It is important for you to keep all appointments with your healthcare provider. Call your healthcare provider if you miss an appointment. There may be special instructions for you.

What are the possible side effects of YERVOY?

YERVOY can cause serious side effects. See "**What is the most important information I should know about YERVOY?**"

The most common side effects of YERVOY include:

- tiredness
- diarrhea
- itching
- rash
- nausea
- vomiting
- headache
- weight loss
- fever
- decreased appetite
- difficulty falling or staying asleep

These are not all of the possible side effects of YERVOY.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Bristol-Myers Squibb at 1-800-721-5072.

General information about the safe and effective use of YERVOY.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your healthcare provider or pharmacist for information about YERVOY that is written for healthcare professionals.

What are the ingredients of YERVOY?

Active ingredient: ipilimumab

Inactive ingredients: diethylene triamine pentaacetic acid (DTPA), mannitol, polysorbate 80, sodium chloride, tris hydrochloride, and Water for Injection, USP

Manufactured by: Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
For more information, call 1-800-321-1335
U.S. License No. 1713
[print code]

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: July 2017