YERVOY® (ipilimumab) injection, for intravenous use

Initial U.S. Approval: 2011

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**INDICATIONS AND USAGE**

**1.1 Unresectable or Metastatic Melanoma**

- 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)

**1.2 Adjuvant Treatment of Melanoma**

- 10 mg/kg administered intravenously over 90 minutes every 3 weeks for 4 doses. (2.1)
- Adjuvant melanoma:
  - 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of 4 doses. (2.1)
  - 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)

**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)

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**ADVERSE REACTIONS**

Most common adverse reactions (≥5%): 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.

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**17 PATIENT COUNSELING INFORMATION**

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2017
2.3 Recommended Dose Modifications

In the event of toxicity, doses are omitted, but all treatment must be administered within 16 weeks of the first dose. 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)].

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, adrenocorticotrophic 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 (ipilimumab) 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

<table>
<thead>
<tr>
<th>Target/Organ System</th>
<th>Adverse Reaction (CTCAE V3)</th>
<th>Treatment Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>Symptomatic endocrinopathy</td>
<td>Withhold YERVOY</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>• Symptomatic reactions lasting 6 weeks or longer</td>
<td>Permanently discontinue YERVOY</td>
</tr>
<tr>
<td></td>
<td>• Inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day</td>
<td></td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td>Grade 2 through 4 reactions</td>
<td>Permanently discontinue YERVOY</td>
</tr>
<tr>
<td></td>
<td>• not improving to Grade 1 within 2 weeks while receiving topical therapy or</td>
<td></td>
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<tr>
<td></td>
<td>• requiring systemic treatment</td>
<td></td>
</tr>
<tr>
<td>All Other</td>
<td>Grade 2</td>
<td>Withhold YERVOY</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>• Grade 2 reactions lasting 6 weeks or longer</td>
<td>Permanently discontinue YERVOY</td>
</tr>
<tr>
<td></td>
<td>• Inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Grade 3 or 4</td>
<td></td>
</tr>
</tbody>
</table>

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.

Permanently discontinue 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 months) and for Grade 2 enterocolitis was 1.4 months (range: 2 days to 4.5 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-corticosteroid 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 transaminases 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 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 dermatis. There were 63 patients (12%) with moderate (Grade 2) dermatitis.

The median time to onset of moderate, severe, or life-threatening immune-mediated dermatis 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 dermatis, 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 dermatis 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) dermatis. The median time to onset for Grade 3 to 4 dermatis was 14 days (range: 5 days to 11.3 months) and for Grade 2 dermatis was 11 days (range: 1 day to 16.6 months).

Sixteen patients (84%) with Grade 3 to 4 dermatis were treated with systemic corticosteroids for a median of 21 days (ranging up to 49.2 months) resulting in complete resolution of dermatis 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 dermatis, 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.

5.3 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 paraesthesia. 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 of prednisone or equivalent for severe neuropathies. Without 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 severe (Grade 3) peripheral motor neuropathy was 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)].

5.4 Immune-Mediated Neopathies
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 hypophysitis 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.

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 (ilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, prematurity 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 nephropathies [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 IIC (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=590), or gp100 peptide vaccine as a single agent (n=132) [see Clinical Studies (4.1)]. Patients in the trial received a median of 4 doses (range: 1 to 4 doses).

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: neoplastic, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemorrhagic 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: 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: angioedema, eczema, myalgia, myositis, pericarditis, pancreatitis, pancytopenia, rash, shortness of breath, Stevens-Johnson syndrome, and acute kidney injury (including adrenal crisis), and hypoglycemia. Patients may present with fever, rash, flu-like symptoms, abdominal pain, unusual bowel habits, 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)].
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 every 3 weeks for 4 doses followed by 10 mg/kg every 12 weeks beginning at Week 24 for 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 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.
YERVOY® (ipilimumab)

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

<table>
<thead>
<tr>
<th>Percentage (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>YERVOY 10 mg/kg n=471</td>
</tr>
<tr>
<td>Any Immune-Mediated Adverse Reaction</td>
</tr>
<tr>
<td>Enteroocolitis a,b</td>
</tr>
<tr>
<td>Hepatitis</td>
</tr>
<tr>
<td>Dermatitis</td>
</tr>
<tr>
<td>Neuropathy a</td>
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<td>Endocrinopathy</td>
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<td>Other</td>
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<td>Myocardiitis a</td>
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<tr>
<td>Meningitis</td>
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<tr>
<td>Pericarditis a</td>
</tr>
<tr>
<td>Pneumonitis</td>
</tr>
<tr>
<td>Uveitis</td>
</tr>
</tbody>
</table>

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.
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.

### 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).

### 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 OVERDOSE

There is no information on overdose 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), sodium chloride (5.85 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 Cmin at steady state was 19.4 mcg/mL at 3 mg/kg and 58.1 mcg/mL at 10 mg/kg every 3 weeks. The mean value (percent coefficient of variation) based on population PK analysis for the terminal half-life (t1/2) was 15.4 days (34%) and for clearance (CL) was 16.8 mL/h (38%).

#### Specific Populations

The effects of various covariates on the PK of ipilimumab were assessed in population PK analyses. The CL of ipilimumab increased with increasing body weight supporting the recommended body weight (mg/kg) based dosing. The following factors had no clinically important effect on the CL of ipilimumab: age (range: 23 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.

### 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.

### 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-A*02:01 or HLA-A*0201 genotype; this HLA genotype facilitates the 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, 25% 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

<table>
<thead>
<tr>
<th></th>
<th>YERVOY</th>
<th>YERVOY+gp100</th>
<th>gp100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio (vs. gp100)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>p-value</td>
<td>(0.51, 0.97)</td>
<td>(0.55, 0.85)</td>
<td>(0.55, 0.85)</td>
</tr>
<tr>
<td>Median (months)</td>
<td>(8.0, 13.8)</td>
<td>(8.5, 11.5)</td>
<td>(5.5, 8.7)</td>
</tr>
</tbody>
</table>

a Not adjusted for multiple comparisons.
### 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 and 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 IIIC with 1 to 3 involved lymph nodes, and 36% had Stage IIIC (with no in-transit metastases). Other disease characteristics of the trial population were:

- 94% had ECOG performance status of 0.
- 62% were male.
- 99% were white.
- 94% had mutation in BRAF.
- 94% had mutation in NRAS.
- 44% had Stage IIIB, 36% had Stage IIIC (with no in-transit metastases).

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 IIIC with 1 to 3 involved lymph nodes, and 36% had Stage IIIC (with no in-transit metastases). Other disease characteristics of the trial population were:

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- 62% were male.
- 99% were white.
- 94% had mutation in BRAF.
- 94% had mutation in NRAS.
- 44% had Stage IIIB, 36% had Stage IIIC (with no in-transit metastases).

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

<table>
<thead>
<tr>
<th>RFS Analysis</th>
<th>YERVOY (N=475)</th>
<th>Placebo (N=476)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Events, n (%)</td>
<td>234 (49%)</td>
<td>294 (62%)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>220</td>
<td>289</td>
</tr>
<tr>
<td>Death</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Median (months)</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(19, 39)</td>
<td>(13, 22)</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.75</td>
<td>1.0</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.64, 0.90)</td>
<td>(0.74, 1.06)</td>
</tr>
<tr>
<td>p-value (stratified log-rank)</td>
<td>p&lt;0.002</td>
<td>0.14</td>
</tr>
</tbody>
</table>

*a Stratified by disease stage.*
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
- pain on the right side of your stomach
- dark urine (tea colored)
- bleeding or bruise more easily than normal
- nausea or vomiting

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.
YERVOY® (ipilimumab)

- 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.

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**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.

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**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.

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**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.

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**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

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

731US1702647-01-01

Bristol-Myers Squibb