The YERVOY® (ipilimumab) Response Assessment Guide

Indication
YERVOY (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma.
Tumor assessment: timing is important

Indication

YERVOY® (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma.

Select Important Safety Information

**WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS**

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

Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests (LFTs) and thyroid function tests at baseline and before each dose.

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

The YERVOY Response Assessment Guide is provided for reference only. Your clinical judgment when using YERVOY is critical for evaluating tumor response.

Please see Important Safety Information, including Boxed WARNING regarding immune-mediated side effects, and accompanying Full Prescribing Information at the end of this document.
Initial assessment of response was conducted at 12 weeks\(^1\)

**YERVOY\(^\circ\) (ipilimumab) 3 mg/kg**
- 1 dose every 3 weeks (×4)

**Dosing period**

**Assessment and follow-up**

**Tumor assessment**
- at weeks 12 and 24 and every 3 months thereafter

Per the pivotal phase 3 study, conduct the initial tumor assessment at week 12, after the conclusion of the dosing period\(^1\)

Ongoing assessment is important to accurately measure response

- In the pivotal phase 3 study, tumor assessments were conducted at week 12, week 24, and every 3 months thereafter\(^1\)
  - Patients with evidence of objective tumor response at week 12 or 24 were assessed for confirmation of durability of response at week 16 or 28, respectively\(^1\)

Please see Important Safety Information, including Boxed WARNING regarding immune-mediated side effects, and accompanying Full Prescribing Information at the end of this document.
Augment T-cell activity with anti-CTLA-4 therapy

YERVOY® (ipilimumab): An anti-CTLA-4 therapy that augments T-cell activation and proliferation, as shown in preclinical studies

- Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a negative regulator of T-cell activation
- Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86
- Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation

The mechanism of action of ipilimumab’s effect in patients with melanoma is indirect, possibly through T-cell–mediated anti-tumor immune responses

- The time to T-cell activation, proliferation, and immune response may vary
  – Therefore, the first tumor assessment was conducted at week 12 in the pivotal phase 3 study

Please see Important Safety Information, including Boxed WARNING regarding immune-mediated side effects, and accompanying Full Prescribing Information at the end of this document.
Each patient’s immune system is unique

It is important to reinforce the following with your patients:

- Each patient’s immune system is unique, so the time course of an individual response to YERVOY® (ipilimumab) may vary.
- The mechanism of action of ipilimumab’s effect in patients with melanoma is indirect, possibly through T-cell–mediated anti-tumor immune responses.
- The YERVOY tumor assessment schedule consists of a tumor assessment at weeks 12 and 24, and every 3 months thereafter. This is based on the timing of tumor assessments in the pivotal phase 3 study.
- Not all patients will respond to YERVOY.

Select Important Safety Information

**WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS**

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Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests (LFTs) and thyroid function tests at baseline and before each dose.

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

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Redefine your treatment goals with durable long-term survival

Median overall survival with YERVOY (ipilimumab) was 10 months\(^1,4,5\)

YERVOY is the only metastatic melanoma therapy proven in a phase 3 study to deliver a durable long-term survival benefit\(^4\)

A phase 3, double-blind, double-dummy study that randomized 676 patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin (IL-2), dacarbazine, temozolomide, fotemustine, or carboplatin. Patients were randomized in a 3:1:1 ratio to receive YERVOY 3 mg/kg in combination with an investigational gp100 peptide vaccine (gp100) (n=403), YERVOY 3 mg/kg (n=137), or gp100 (n=136). The primary endpoint was overall survival in the YERVOY + gp100 arm vs the gp100 arm.\(^4\)

The YERVOY overall survival curve separated at approximately 16 weeks and remained separated throughout the study period, demonstrating a higher overall survival benefit compared to the control arm.\(^5\)

The Kaplan-Meier survival curve illustrates the proportion of patients alive over time:

- YERVOY + gp100 vs gp100: HR=0.68 (95% CI: 0.55, 0.85), \(P=0.0004\)
- YERVOY vs gp100: HR=0.66 (95% CI: 0.51, 0.87), \(P=0.0026\)

\(24\%\quad 2\text{-YEAR survival rate}\)\(^1,4\)

\(*\)Estimate based on Kaplan-Meier analysis.

Some patients were still alive up to 4.5 YEARS\(^1,4\)

\(*\)The overall survival curve shows 2, 1, and 0 patients were still in follow-up in the YERVOY arm at 48, 52, and 56 months at the time of study closure.

*Please see Important Safety Information, including Boxed WARNING regarding immune-mediated side effects, and accompanying Full Prescribing Information at the end of this document.*
**YERVOY® (ipilimumab) may provide a lasting benefit**

**YERVOY responders (CR or PR) demonstrated durable responses**

<table>
<thead>
<tr>
<th>Response with YERVOY vs gp100&lt;sup&gt;4&lt;/sup&gt;</th>
<th>YERVOY n=137</th>
<th>YERVOY + gp100 n=403</th>
<th>gp100 n=136</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of responders (CR + PR)</td>
<td>15</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Best overall response rate (95% CI)</td>
<td>10.9% (6.3%, 17.4%)</td>
<td>5.7% (3.7%, 8.4%)</td>
<td>1.5% (0.2%, 5.2%)</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>2 (1.5%)</td>
<td>1 (0.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>13 (9.5%)</td>
<td>22 (5.5%)</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Median duration of response (95% CI)</td>
<td>Not reached (28.1, not reached)</td>
<td>11.5 months (5.4, not reached)</td>
<td>Not reached (2.0, not reached)</td>
</tr>
</tbody>
</table>

**Select Important Safety Information**

**Overall Study Safety**

- In patients who received 3 mg/kg YERVOY alone (n=131), severe to fatal immune-mediated adverse reactions were reported and included enterocolitis (7%), endocrinopathy (4%, all of which had hypopituitarism), dermatitis (2%), hepatotoxicity (1%), neuropathy (1%), nephritis (1%), and eosinophilia (1%)
- In patients who received 3 mg/kg of YERVOY + gp100 (n=380), severe to fatal immune-mediated adverse reactions were reported and included enterocolitis (7%), hepatotoxicity (2%), dermatitis (3%), endocrinopathy (1%, hypopituitarism, 1% adrenal insufficiency), neuropathy (<1%), pneumonitis (<1%), meningitis (<1%), pericarditis (<1%)
- The most common adverse reactions were fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%) for the YERVOY alone arm, diarrhea (37%), fatigue (34%), rash (25%), pruritus (21%), and colitis (5%) for the YERVOY + gp100 arm, and fatigue (31%), diarrhea (20%), pruritus (11%), rash (8%), and colitis (2%) for gp100 arm. YERVOY therapy was discontinued for adverse reactions in 10% of patients
Please see Important Safety Information, including **Boxed WARNING regarding immune-mediated side effects**, and accompanying Full Prescribing Information at the end of this document.

**References:**

To learn more about YERVOY (ipilimumab), please visit www.YERVOY.com.

Please see Important Safety Information, including Boxed WARNING regarding immune-mediated side effects, and accompanying Full Prescribing Information at the end of this document.

Bristol-Myers Squibb
Important Safety Information

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

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

Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests (LFTs) and thyroid function tests at baseline and before each dose.

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

Recommended Dose Modifications

Withhold dose for any moderate immune-mediated adverse reactions or for symptomatic endocrinopathy until return to baseline, improvement to mild severity, or complete resolution, and patient is receiving <7.5 mg prednisone or equivalent per day.

Permanently discontinue YERVOY for any of the following:

- Persistent moderate adverse reactions or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day
- Failure to complete full treatment course within 16 weeks from administration of first dose
- Severe or life-threatening adverse reactions, including any of the following:
  - Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (≥7 over baseline), stool incontinence, need for intravenous hydration for >24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation
  - AST or ALT >5x the upper limit of normal (ULN) or total bilirubin >3x the ULN
  - Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full-thickness dermal ulceration or necrotic, bullous, or hemorrhagic manifestations
  - Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
  - Severe immune-mediated reactions involving any organ system
  - Immune-mediated ocular disease which is unresponsive to topical immunosuppressive therapy

Immune-mediated Enterocolitis:

- In the pivotal Phase 3 study in YERVOY-treated patients, severe, life-threatening, or fatal (diarrhea of ≥7 stools above baseline, fever, ileus, peritoneal signs; Grade 3-5) immune-mediated enterocolitis occurred in 34 (7%) and moderate (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) enterocolitis occurred in 28 (5%) patients
- Across all YERVOY-treated patients (n=511), 5 (1%) developed intestinal perforation, 4 (0.8%) died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis
- Infliximab was administered to 5 of 62 (8%) patients with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids
- 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 (1-2 mg/kg/day of prednisone or equivalent). Upon improvement to ≤Grade 1, initiate corticosteroid taper and continue over at least 1 month. In clinical trials, rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients
- Withhold YERVOY for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for >1 week, initiate systemic corticosteroids (0.5 mg/kg/day prednisone or equivalent)

Immune-mediated Hepatitis:

- In the pivotal Phase 3 study in YERVOY-treated patients, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations >5x the ULN or total bilirubin elevations >3x the ULN; Grade 3-5) occurred in 8 (2%) patients, with fatal hepatic failure in 0.2% and hospitalization in 0.4%
- 13 (2.5%) additional YERVOY-treated patients experienced moderate hepatotoxicity manifested by LFT abnormalities (AST or ALT elevations >2.5x but ≤5x the ULN or total bilirubin elevation >1.5x but ≤3x the ULN; Grade 2)
- Monitor LFTs (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 LFT monitoring until resolution

Continued on next page.

Please see Full Prescribing Information, including Boxed WARNING regarding immune-mediated side effects, at the end of this document.
• Permanently discontinue YERVOY® (ipilimumab) in patients with Grade 3-5 hepatotoxicity and administer systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). When LFTs show sustained improvement or return to baseline, initiate corticosteroid tapering and continue over 1 month. Across the clinical development program for YERVOY, mycophenolate treatment has been administered in patients with persistent severe hepatitis despite high-dose corticosteroids
• Withhold YERVOY in patients with Grade 2 hepatotoxicity
• 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)

Immune-mediated Dermatitis:
• In the pivotal Phase 3 study in YERVOY-treated patients, 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 3-5) occurred in 13 (2.5%) patients
  – 1 (0.2%) patient died as a result of toxic epidermal necrolysis
  – 1 additional patient required hospitalization for severe dermatitis
• There were 63 (12%) YERVOY-treated patients with moderate (Grade 2) dermatitis
• 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 severe, life-threatening, or fatal immune-mediated dermatitis (Grade 3-5). Administer systemic corticosteroids (1-2 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 in patients with moderate to severe signs and symptoms
• Treat mild to moderate dermatitis (e.g., localized rash and pruritus) symptomatically. Administer topical or systemic corticosteroids if there is no improvement within 1 week

Immune-mediated Neuropathies:
• In the pivotal Phase 3 study in YERVOY-treated patients, 1 case of fatal Guillain-Barré syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported
• Across the clinical development program of YERVOY, myasthenia gravis and additional cases of Guillain-Barré syndrome have been reported
• Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Permanently discontinue YERVOY in patients with severe neuropathy (interfering with daily activities) such as Guillain-Barré–like syndromes
• Institute medical intervention as appropriate for management of severe neuropathy. Consider initiation of systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe neuropathies. Withhold YERVOY in patients with moderate neuropathy (not interfering with daily activities)

Immune-mediated Endocrinopathies:
• In the pivotal Phase 3 study in YERVOY-treated patients, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3-4) occurred in 9 (1.8%) patients
  – All 9 patients had hypopituitarism, and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism
  – 6 of the 9 patients were hospitalized for severe endocrinopathies
• Moderate endocrinopathy (requiring hormone replacement or medical intervention; Grade 2) occurred in 12 (2.3%) YERVOY-treated patients and consisted of hypothyroidism, adrenal insufficiency, hypopituitarism, and 1 case each of hyperthyroidism and Cushing's syndrome
• Median time to onset of moderate to severe immune-mediated endocrinopathy was 11 weeks and ranged up to 19.3 weeks after the initiation of YERVOY
• 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 should be considered immune-mediated
  – Monitor thyroid function tests and clinical chemistries at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland
• Withhold YERVOY in symptomatic patients. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) and initiate appropriate hormone replacement therapy. Long-term hormone replacement therapy may be necessary

Continued on next page.

Please see Full Prescribing Information, including Boxed WARNING regarding immune-mediated side effects, at the end of this document.
Other Immune-mediated Adverse Reactions, Including Ocular Manifestations:

- In the pivotal Phase 3 study in YERVOY® (ipilimumab)-treated patients, clinically significant immune-mediated adverse reactions seen in <1% were: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia.
- Across the clinical development program for YERVOY, likely immune-mediated adverse reactions also reported with <1% incidence were: myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, autoimmune thyroiditis, sarcoidosis, neurosensory hypoacusis, autoimmune central neuropathy (encephalitis), myositis, polymyositis, and ocular myositis.
- Permanently discontinue YERVOY for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe immune-mediated adverse reactions.
- Administer corticosteroid eye drops for uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease unresponsive to local immunosuppressive therapy.

Pregnancy & Nursing:

- YERVOY is classified as pregnancy category C. There are no adequate and well-controlled studies of YERVOY in pregnant women. Use YERVOY during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Human IgG1 is known to cross the placental barrier and YERVOY is an IgG1; therefore, YERVOY has the potential to be transmitted from the mother to the developing fetus.
- It is not known whether YERVOY is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from YERVOY, a decision should be made whether to discontinue nursing or to discontinue YERVOY.

Common Adverse Reactions:

- The most common adverse reactions (≥5%) in patients who received YERVOY at 3 mg/kg were fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%).

Please see Full Prescribing Information, including Boxed WARNING regarding immune-mediated side effects, at the end of this document.
YERVOY® (ipilimumab)
Injection, for intravenous infusion
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 due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.
Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions. (2.2)
Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests and thyroid function tests at baseline and before each dose. (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 the treatment of unresectable or metastatic melanoma. (1)

DOSAGE AND ADMINISTRATION
• YERVOY 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of four doses. (2.1)
• Permanently discontinue for severe adverse reactions. (2.2)

Dosage forms and strengths
• 50 mg/10 mL (5 mg/mL) (3)
• 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 (ipilimumab). (5.2)
• Immune-mediated endocrinopathies: Monitor thyroid function tests and clinical chemistries prior to each dose. Evaluate at each visit for signs and symptoms of endocrinopathy. Institute hormone replacement therapy as needed. (5.5)

ADVERSE REACTIONS
Most common adverse reactions (≥5%) are fatigue, diarrhea, pruritus, rash, and colitis. (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
• Pregnancy: Based on animal data, YERVOY may cause fetal harm. (8.1)
• Nursing mothers: Discontinue nursing or discontinue YERVOY. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

DRUG INTERACTIONS

USE IN SPECIFIC POPULATIONS

Pregnancy

Nursing Mothers

Pediatric Use

Geriatric Use

Renal Impairment

Hepatic Impairment

OVERDOSAGE

CLINICAL PHARMACOLOGY

Mechanism of Action

Pharmacokinetics

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal Toxicology and/or Pharmacology

CLINICAL STUDIES

HOW SUPPLIED/STORAGE AND HANDLING

PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.
The recommended dose of YERVOY is 3 mg/kg administered intravenously over 2.1 Recommended Dosing

YERVOY (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma.

INDICATIONS AND USAGE

• Discard partially used vials or empty vials of YERVOY.
• Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 0.1 mg/mL to 1 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.

Dosage and Administration

1 INDIcATIONS AND USAGE

YERVOY (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

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

2.2 Recommended Dose Modifications

• Withhold scheduled dose of YERVOY for any moderate immune-mediated adverse reactions or for symptomatic endocrinopathy. For patients with complete or partial resolution of adverse reactions (Grade 0–1), and who are receiving less than 7.5 mg prednisone or equivalent per day, resume YERVOY at a dose of 3 mg/kg every 3 weeks until administration of all 4 planned doses or 16 weeks from first dose, whichever occurs earlier.

• Permanently discontinue YERVOY for any of the following:
  o Persistent moderate adverse reactions or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.
  o Failure to complete full treatment course within 16 weeks from administration of first dose.
  o Severe or life-threatening adverse reactions, including any of the following:
    ▪ Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation
    ▪ Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times the upper limit of normal or total bilirubin >3 times the upper limit of normal
    ▪ Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations
    ▪ Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
    ▪ Severe immune-mediated reactions involving any organ system (eg, nephritis, pneumonitis, pancreatitis, non-infectious mycarditis)
    ▪ Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy

2.3 Preparation and Administration

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

Preparation of Solution

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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

5.1 Immune-mediated Enterocolitis

In Study 1, severe, life-threatening, or fatal (diarrhea of 7 or more stools above baseline, fever, ileus, peritoneal signs; Grade 3–5) immune-mediated enterocolitis occurred in 34 (7%) YERVOY-treated patients, and moderate (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) enterocolitis occurred in 28 (5%) YERVOY-treated patients. Across all YERVOY-treated patients (n=511), 5 (1%) patients developed intestinal perforation, 4 (0.8%) patients died as a result of complications, and 26 (5%) patients were hospitalized for severe enterocolitis.

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

Twenty-nine patients (85%) with Grade 3–5 enterocolitis were treated with high-dose (>40 mg prednisone equivalent per day) corticosteroids, with a median dose of 80 mg/day of prednisone or equivalent; the median duration of treatment was 2.3 weeks (ranging up to 13.9 weeks) followed by corticosteroid taper. Of the 28 patients with moderate enterocolitis, 46% were not treated with systemic corticosteroids, 20% were treated with <40 mg prednisone or equivalent per day for a median duration of 5.1 weeks, and 25% were treated with high-dose corticosteroids for a median duration of 10 days prior to corticosteroid taper. Infliximab was administered to 5 of the 62 patients (8%) with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids.

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

Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). 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.

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

5.2 Immune-mediated Hepatitis

In Study 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 3–5) occurred in 8 (2%) YERVOY-treated patients, with fatal hepatic failure in 0.2% and hospitalization in 0.4% of YERVOY-treated patients. An additional 13 (2.5%) patients experienced moderate hepatotoxicity manifested by liver function test abnormalities (AST or ALT elevations of more than 2.5 times but not more than 5 times the upper limit of normal or total bilirubin elevation of more than 1.5 times but not more than 3 times the upper limit of normal; Grade 2). The underlying pathology was not ascertained in all patients but in some instances included immune-mediated hepatitis. There were insufficient numbers of patients with biopsy-proven hepatitis to characterize the clinical course of this event.

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

Permanently discontinue YERVOY in patients with Grade 3–5 hepatotoxicity and administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When liver function tests show sustained improvement or return to baseline, initiate corticosteroid tapering and continue to taper over 1 month. Across the clinical development program for YERVOY, mycophenolate treatment has been administered in patients who have persistent severe hepatitis despite high-dose corticosteroids. Withhold YERVOY in patients with Grade 2 hepatotoxicity. [See Dosage and Administration (2.2).]
YERVOY® (ipilimumab)

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 Dermatitiss

In Study 1, severe, life-threatening, or fatal immune-mediated dermatitis (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3–5) occurred in 13 (2.5%) YERVOY-treated patients. One (0.2%) patient died as a result of toxic epidermal necrolysis and one additional patient required hospitalization for severe dermatitis. There were 63 (12%) patients with moderate (Grade 2) dermatitis.

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

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

Of the 63 patients with moderate dermatitis, 25 (40%) were treated with systemic corticosteroids (median of 60 mg/day of prednisone or equivalent) for a median of 2.1 weeks, 7 (11%) were treated with only topical corticosteroids, and 31 (49%) did not receive systemic or topical corticosteroids. Forty-four (70%) patients with moderate dermatitis were reported to have complete resolution, 7 (11%) improved to mild (Grade 1) severity, and 12 (19%) had no reported improvement.

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

Permanently discontinue YERVOY in patients with Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations. Administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month.

Withhold YERVOY dosing in patients with moderate to severe signs and symptoms. [See Dosage and Administration (2.2).]

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

5.4 Immune-mediated Neuropathies

In Study 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.

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 of prednisone or equivalent for severe neuropathies. Withhold YERVOY dosing in patients with moderate neuropathy (not interfering with daily activities). [See Dosage and Administration (2.2).]

5.5 Immune-mediated Endocrinopathies

In Study 1, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3–4) occurred in 9 (1.8%) YERVOY-treated patients. All 9 patients had hypothyroidism and some had additional concomitant endocrinopathies such as adrenal insufficiency, hyperglycemia, and hypophysitis. Six of the 9 patients were hospitalized for severe endocrinopathies. Moderate endocrinopathy (requiring hormone replacement or medical intervention; Grade 2) occurred in 12 (2.3%) patients and consisted of hypothyroidism, adrenal insufficiency, hypophysitis, and 1 case each of hyperthyroidism and Cushing’s syndrome. The median time to onset of moderate to severe immune-mediated endocrinopathy was 11 weeks and ranged up to 19.3 weeks after the initiation of YERVOY.

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

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

Monitor thyroid function tests and clinical chemistries at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland.

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

5.6 Other Immune-mediated Adverse Reactions, Including Ocular Manifestations

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

Across the clinical development program for YERVOY, the following likely immune-mediated adverse reactions were also reported with less than 1% incidence: myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclastic vasculitis, erythema multiforme, psooriasis, panarteritis, arthritis, autoimmune thyroiditis, sarcoidosis, neurosensory hypoacusis, autoimmune central neuropathy (encephalitis), myositis, polyarthitis, and ocular myositis.

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 (2.2).]

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 neutropheties [see Warnings and Precautions (5.4)].
- Immune-mediated endocrinopathies [see Warnings and Precautions (5.5)].
- Other immune-mediated adverse reactions, including ocular manifestations [see Warnings and Precautions (5.6)].

6.1 Clinical Trials Experience

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

The clinical development program excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation. Exposure to YERVOY 3 mg/kg for 4 doses given by intravenous infusion in previously treated patients with unresectable or metastatic melanoma was assessed in a randomized, double-blind clinical study (Study 1). [See Clinical Studies (14).] One hundred thirty-one patients (median age 57 years, 60% male) received YERVOY as a single agent, 380 patients (median age 56 years, 61% male) received YERVOY with an investigational gp100 peptide vaccine (gp100), and 132 patients (median age 57 years, 54% male) received gp100 peptide vaccine alone. Patients in the study received a median of 4 doses (range: 1–4 doses). YERVOY was discontinued for adverse reactions in 10% of patients.

The most common adverse reactions (>5%) in patients who received YERVOY at 3 mg/kg were fatigue, diarrhea, pruritus, rash, and colitis.

Table 1 presents selected adverse reactions from Study 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 3–5 events.

Table 1: Selected Adverse Reactions in Study 1

<table>
<thead>
<tr>
<th>System Organ Class/Preferred Term</th>
<th>YERVOY 3 mg/kg</th>
<th>YERVOY 3 mg/kg+gp100</th>
<th>gp100 n=132</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Colitis</td>
<td>8</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>31</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Rash</td>
<td>29</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>41</td>
<td>3</td>
<td>31</td>
</tr>
</tbody>
</table>

a Incidences presented in this table are based on reports of adverse events regardless of causality.
YERVOY® (ipilimumab)

Table 2 presents the per-patient incidence of severe, life-threatening, or fatal immune-mediated adverse reactions from Study 1.

<table>
<thead>
<tr>
<th>Any Immune-mediated Adverse Reaction</th>
<th>YERVOY 3 mg/kg</th>
<th>YERVOY 3 mg/kg × 100</th>
<th>Percentage (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterocolitis&lt;sup&gt;2&lt;/sup&gt;</td>
<td>15</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Enterotoxicity&lt;sup&gt;2&lt;/sup&gt;</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Hepatotoxicity&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Dermatitis&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Neuroopathy&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Endocrinopathy</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>0</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Nephritis</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Eosinophilia&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pericarditis&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

<sup>2</sup> Including fatal outcome.

<sup>3</sup> Including intestinal perforation.

<sup>4</sup> Underlying etiology not established.

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 infusional reaction.

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

6.2 Immunogenicity

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

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

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

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of YERVOY in pregnant women. Use YERVOY during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In a combined study of embryo-fetal and peri-natal development, pregnant cynomolgus monkeys received ipilimumab every 3 weeks from the onset of organogenesis in the first trimester through parturition, at exposure levels either 2.6 or 7.2 times higher by AUC than the exposures at the clinical dose of 3 mg/kg of ipilimumab. No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, the ipilimumab-treated groups experienced higher incidences of severe toxicities including abortion, stillbirth, prematurity delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner compared to controls. [See Nonclinical Toxicology (13.2)].

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

8.2 Pediatric Use

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

8.3 Nursing Mothers

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

8.4 Geriatric Use

Of the 511 patients treated with YERVOY at 3 mg/kg, 28% were 65 years and over. No overall differences in safety or efficacy were reported between the elderly patients (65 years and over) and younger patients (less than 65 years).

8.6 Renal Impairment

No dose adjustment is needed for patients with renal impairment. [See Clinical Pharmacology (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 x the upper limit of normal [ULN] or AST >ULN). YERVOY has not been studied in patients with moderate (TB >1.5 to 3.0 x ULN and any AST) or severe (TB >3 x 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 particulate. 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 (0.1 mg), sodium chloride (5.85 mg), triis(hydroxymethyl)aminomethane (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 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 particulate. 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 (0.1 mg), sodium chloride (5.85 mg), triis(hydroxymethyl)aminomethane (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 effector function, including the anti-tumor immune response.

12.3 Pharmacokinetics

The pharmacokinetics of ipilimumab were studied in 785 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg once every 3 weeks for 4 doses. Peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration versus time curve (AUC) of ipilimumab increased dose proportionally within the dose range examined. Upon repeated dosing every 3 weeks, the clearance (CL) of ipilimumab was found to be time-invariant, and systemic accumulation was 1.5-fold or less. Steady-state concentrations of ipilimumab were reached by the third dose; the mean Cmin at steady-state was 19.4 mcg/mL following repeated doses of 3 mg/kg. The mean value (% coefficient of variation) generated through population pharmacokinetic analysis for the terminal half-life (t1/2) was 15.4 days (34%) and for CL was 16.8 mL/h (38%)

**Specific Populations:** The effects of various covariates on the pharmacokinetics of ipilimumab were assessed in population pharmacokinetic analyses. The CL of ipilimumab increased with increasing body weight; however, no dose adjustment is recommended for body weight after administration on a mg/kg basis. The following factors had no clinically important effect on the CL of ipilimumab: age (range: 23–88 years), gender, performance status, renal impairment, mild hepatic impairment, previous cancer therapy, and baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined due to limited data available in non-Caucasian ethnic groups.

**Renal Impairment:** The effect of renal impairment on the CL of ipilimumab was evaluated in patients with mild (GFR <90 and ≥60 mL/min/1.73 m²; n=349), moderate (GFR <60 and ≥30 mL/min/1.73 m²; n=82), or severe (GFR <30 and ≥15 mL/min/1.73 m²; n=4) renal impairment compared to patients with normal renal function (GFR ≥90 mL/min/1.73 m², n=350) in population pharmacokinetic analyses. No clinically important differences in the CL of ipilimumab were found between patients with renal impairment and patients with normal renal function. [See Use in Specific Populations (8.6).]
Hepatic Impairment: The effect of hepatic impairment on the CL of ipilimumab was evaluated in patients with mild hepatic impairment (TB 1.0 x to 1.5 x ULN or AST >ULN) and normal hepatic function (TB and AST ≤ULN; n=708) in the population pharmacokinetic analyses. No clinically important differences in the CL of ipilimumab were found between patients with mild hepatic impairment and normal hepatic function. YERVOY has not been studied in patients with moderate (TB >1.5 x to 3 x ULN and any AST) or severe hepatic impairment (TB >3 x ULN and any AST). [See Use in Specific Populations (8.7).]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

The genotoxic potential of ipilimumab has not been evaluated.

Impairment of Fertility

Fertility studies have not been performed with ipilimumab.

13.2 Animal Toxicology and/or Pharmacology

In addition to the severe findings of abortion, stillbirths, and postnatal deaths observed in pregnant cynomolgus monkeys that received ipilimumab every 3 weeks from the onset of organogenesis in the first trimester through parturition [see Use in Specific Populations (8.1)], developmental abnormalities were identified in the urogenital system of 2 infant monkeys exposed to ipilimumab at 30 mg/kg on gestational day 7.2 times the AUC in humans at the clinically recommended dose. One female infant monkey had unilateral renal agenesis of the left kidney and ureter, and a male infant monkey had an imperforate urethra with associated urinary obstruction and subcutaneous scrotal edema.

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

14 CLINICAL STUDIES

The safety and efficacy of YERVOY were investigated in a randomized (3:1:1), double-blind, double-dummy study (Study 1) that included 676 randomized patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. Of these 676 patients, 403 were randomized to receive YERVOY at 3 mg/kg in combination with an investigational peptide vaccine. The study excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation. YERVOY/placebo was administered at 3 mg/kg as an intravenous infusion every 3 weeks for 4 doses. Gp100/placebo was administered at a dose of 2 mg peptide by deep subcutaneous injection every 3 weeks for 4 doses. Assessment of tumor response was conducted at weeks 12 and 24, and every 3 months thereafter. Patients with evidence of objective tumor response at 12 or 24 weeks had assessment for confirmation of durability of response at 16 or 28 weeks, respectively.

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

Of the randomized patients, 61%, 59%, and 54% in the YERVOY+gp100, YERVOY, and gp100 arms, respectively, were men. Twenty-nine percent were ≥65 years of age, the median age was 57 years, 71% had M1c stage, 12% had a history of previously treated brain metastasis, 98% had ECOG performance status of 0 and 1, 23% had received adjuvant, 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 3 and Figure 1.

<table>
<thead>
<tr>
<th></th>
<th>YERVOY</th>
<th>YERVOY+gp100</th>
<th>gp100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio</td>
<td>0.66</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.51, 0.87)</td>
<td>(0.55, 0.85)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0026</td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td>Median (months)</td>
<td></td>
<td>(8.0, 13.8)</td>
<td>(8.5, 11.5)</td>
</tr>
</tbody>
</table>

* Not adjusted for multiple comparisons.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

YERVOY is available as follows:

- One 200 mg vial (5 mg/mL), single-use vial
- One 50 mg vial (5 mg/mL), single-use vial

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).

- Inform patients of the potential risk of immune-mediated adverse reactions.
- Advise patients to read the YERVOY Medication Guide before each YERVOY infusion.
- Advise women that YERVOY may cause fetal harm.
- Advise nursing mothers not to breastfeed while taking YERVOY.

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

1321675A1 Rev March 2015
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 side effects are most likely to begin during treatment; however, side effects can show up months after your last infusion.

These side effects may include:

1. **Inflammation of the intestines (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

2. **Inflammation of the liver (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

3. **Inflammation of the skin that can lead to severe skin reaction (toxic epidermal necrolysis).** Signs and symptoms of severe skin reactions may include:
   - skin rash with or without itching
   - sores in your mouth
   - your skin blisters and/or peels

4. **Inflammation of the nerves 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

5. **Inflammation of hormone glands (especially the pituitary, adrenal, and thyroid glands) that may affect how these glands work.** Signs and symptoms that your glands are not working properly may include:
   - persistent or unusual headaches
   - unusual sluggishness, feeling cold all the time, or weight gain
   - changes in mood or behavior such as decreased sex drive, irritability, or forgetfulness
   - dizziness or fainting

6. **Inflammation of the eyes.** Symptoms may include:
   - blurry vision, double vision, or other vision problems
   - eye pain or redness

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

Getting medical treatment right away may keep the problem from becoming more serious. Your oncologist may decide to delay or stop YERVOY.

What is YERVOY?

YERVOY is a prescription medicine used in adults to treat melanoma (a kind of skin cancer) that has spread or cannot be removed by surgery.

It is not known if YERVOY is safe and effective in children less than 18 years of age.

What should I tell my healthcare provider before getting YERVOY?

Before you are given YERVOY, tell your healthcare provider about all your health problems if you:

- have an active condition where your immune system attacks your body (autoimmune disease), such as ulcerative colitis, Crohn's disease, lupus, or sarcoidosis
YERVOY® (ipilimumab)

- had an organ transplant, such as a kidney transplant
- have liver damage from diseases or drugs
- have any other medical conditions
- are pregnant or plan to become pregnant. YERVOY may cause stillbirth, premature delivery, and/or death of your unborn baby
- are breastfeeding

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, steroids or other medicines that lower your immune response, vitamins, and herbal supplements.

Know the medicines you take. Keep a list to show your doctors and pharmacists each time you get a new medicine.

You should not start a new medicine before you talk with the healthcare provider who prescribes you YERVOY.

How will I receive YERVOY?

You will get YERVOY through an intravenous line in your vein (infusion). It takes about 90 minutes to get a full dose.

- YERVOY is usually given every 3 weeks for up to 4 doses. Your healthcare provider may change how often you receive YERVOY or how long the infusion may take.
- Your healthcare provider should perform 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

These are not all of the possible side effects of YERVOY. For more information, ask your healthcare provider.

Call your healthcare provider 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.

This Medication Guide summarizes the most important information about YERVOY. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider for information about YERVOY that is written for healthcare professionals.

For more information, call 1-800-321-1335.

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

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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