

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125377Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

YERVOY™ (ipilimumab)
Injection, for intravenous 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)

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- 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.
- 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.

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

Revised: March 2011

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FULL PRESCRIBING 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.

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

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

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of YERVOY is 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of four 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:
 - Persistent moderate adverse reactions or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.
 - Failure to complete full treatment course within 16 weeks from administration of first dose.
 - Severe or life-threatening adverse reactions, including any of the following:
 - Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation
 - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times the upper limit of normal or total bilirubin >3 times the upper limit of normal
 - Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations
 - Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
 - Severe immune-mediated reactions involving any organ system (eg, nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)
 - Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy

2.3 Preparation and Administration

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

Preparation of Solution

- Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
- Withdraw the required volume of YERVOY and transfer into an intravenous bag.
- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.
- Store the diluted solution for no more than 24 hours under refrigeration (2°C to 8°C, 36°F to 46°F) or at room temperature (20°C to 25°C, 68°F to 77°F).
- Discard partially used vials or empty vials of YERVOY.

Administration Instructions

- Do not mix YERVOY with, or administer as an infusion with, other medicinal products.
- Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 0.5% Dextrose Injection, USP after each dose.
- Administer diluted solution over 90 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.

3 DOSAGE FORMS AND STRENGTHS

50 mg/10 mL (5 mg/mL).

200 mg/40 mL (5 mg/mL).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

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

5.1 Immune-mediated Enterocolitis

In Study 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, 29% were treated with < 40 mg prednisone or equivalent per day for a median duration of 5.1 weeks, and 25% were treated with high-dose corticosteroids for a median duration of 10 days prior to corticosteroid taper. Infliximab was administered to 5 of the 62 patients (8%) with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids.

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

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

5.3 Immune-mediated Dermatitis

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, one case of fatal Guillain-Barré syndrome and one case of severe (Grade 3) peripheral motor neuropathy were reported. Across the clinical development program of

YERVOY, myasthenia gravis and additional cases of Guillain-Barré syndrome have been reported.

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

5.5 Immune-mediated Endocrinopathies

In Study 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 hypopituitarism and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies. Moderate endocrinopathy (requiring hormone replacement or medical intervention; Grade 2) occurred in 12 (2.3%) patients and consisted of hypothyroidism, adrenal insufficiency, hypopituitarism, and one 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, psoriasis, pancreatitis, arthritis, and autoimmune thyroiditis.

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

6.1 Clinical Trials Experience

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

The clinical development program excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation. Exposure to YERVOY 3 mg/kg for four 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 to 4 doses). YERVOY was discontinued for adverse reactions in 10% of patients.

The most common adverse reactions ($\geq 5\%$) 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

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

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

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

Table 2: Severe to Fatal Immune-mediated Adverse Reactions in Study 1

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

^a Including fatal outcome.

^b Including intestinal perforation.

^c Underlying etiology not established.

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.

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 drug-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-postnatal development, severe toxicities including increased incidences of third-trimester abortion, stillbirth, premature delivery, low birth weight, and infant mortality occurred following intravenous administration of ipilimumab to pregnant cynomolgus monkeys every 21 days from the onset of organogenesis through parturition at doses of 2.6 or 7.2 times the recommended human dose of 3 mg/kg (by AUC). [See [Nonclinical Toxicology \(13.2\)](#)]

In genetically engineered mice in which the gene for CTLA-4 has been deleted (a “knockout mouse”), offspring lacking CTLA-4 were born apparently healthy, but died within 3–4 weeks due to multi-organ infiltration and damage by lymphocytes.

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

8.3 Nursing Mothers

It is not known whether ipilimumab is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from YERVOY, a decision should be made whether to discontinue nursing or to discontinue YERVOY, taking into account the importance of YERVOY to the mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

No formal studies of YERVOY in patients with renal impairment have been conducted. *[See Clinical Pharmacology (12.3)]*

8.7 Hepatic Impairment

No formal studies of YERVOY in patients with hepatic impairment have been conducted. *[See Clinical Pharmacology (12.3)]*

10 OVERDOSAGE

There is no information on overdosage with YERVOY.

11 DESCRIPTION

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CTLA-4 is a negative regulator of T-cell 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.

12.3 Pharmacokinetics

The pharmacokinetics of ipilimumab was studied in 499 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg administered once every 3 weeks for four doses. Peak concentration (C_{max}), trough concentration (C_{min}), and area under the curve (AUC) of ipilimumab were found to be dose proportional within the dose range examined. Upon repeated dosing of YERVOY administered every 3 weeks, ipilimumab clearance was found to be time-invariant, and minimal systemic accumulation was observed as evident by an accumulation index of 1.5-fold or less. Ipilimumab steady-state concentration was reached by the third dose. The following mean (percent coefficient of variation) parameters were generated through population pharmacokinetic analysis: terminal half-life of 14.7 days (30.1%); systemic clearance (CL) of 15.3 mL/h (38.5%); and volume of distribution at steady-state (V_{ss}) of 7.21 L (10.5%). The

mean (\pm SD) ipilimumab C_{\min} achieved at steady-state with the 3-mg/kg regimen was 21.8 mcg/mL (\pm 11.2).

Specific Populations: Cross-study analyses were performed on data from patients with a variety of conditions, including 420 patients with melanoma who received single or multiple infusions of YERVOY at doses of 0.3, 3, or 10 mg/kg. The effects of various covariates on ipilimumab pharmacokinetics were assessed in population pharmacokinetic analyses.

Ipilimumab CL increased with increasing body weight; however, no dose adjustment of YERVOY is required for body weight after administration on a mg/kg basis. The following factors had no clinically meaningful effect on the CL of ipilimumab: age (range 26 to 86 years), gender, concomitant use of budesonide, performance status, HLA-A2*0201 status, positive anti-ipilimumab antibody status, prior use of systemic anticancer therapy, or baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined as there were insufficient numbers of patients in non-Caucasian ethnic groups.

Renal Impairment: Creatinine clearance at baseline did not have a clinically important effect on ipilimumab pharmacokinetics in patients with calculated creatinine clearance values of 29 mL/min or greater.

Hepatic Impairment: Baseline AST, total bilirubin, and ALT levels did not have a clinically important effect on ipilimumab pharmacokinetics in patients with various degrees of hepatic impairment.

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

The effects of ipilimumab on prenatal and postnatal development in monkeys have not been fully investigated. Preliminary results are available from an ongoing study in cynomolgus monkeys. Pregnant monkeys received ipilimumab every 21 days from the onset of organogenesis in the first trimester through delivery, at dose levels either 2.6 or 7.2 times higher than the clinical dose of 3 mg/kg of ipilimumab (by AUC). No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, the ipilimumab groups experienced higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner compared to controls.

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 with incomplete Freund's adjuvant (gp100), 137 were randomized to receive YERVOY at 3 mg/kg, and 136 were randomized to receive gp100 alone. The study enrolled only patients with HLA-A2*0201 genotype; this HLA genotype facilitates the immune presentation of the investigational peptide vaccine. The study excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation. YERVOY/placebo was administered at 3 mg/kg as an intravenous infusion every 3 weeks for four doses. Gp100/placebo was administered at a dose of 2 mg peptide by deep subcutaneous injection every 3 weeks for four doses. Assessment of tumor response was conducted at weeks 12 and 24, and every 3 months thereafter. Patients with evidence of objective tumor response at 12 or 24 weeks had assessment for confirmation of durability of response at 16 or 28 weeks, respectively.

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

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

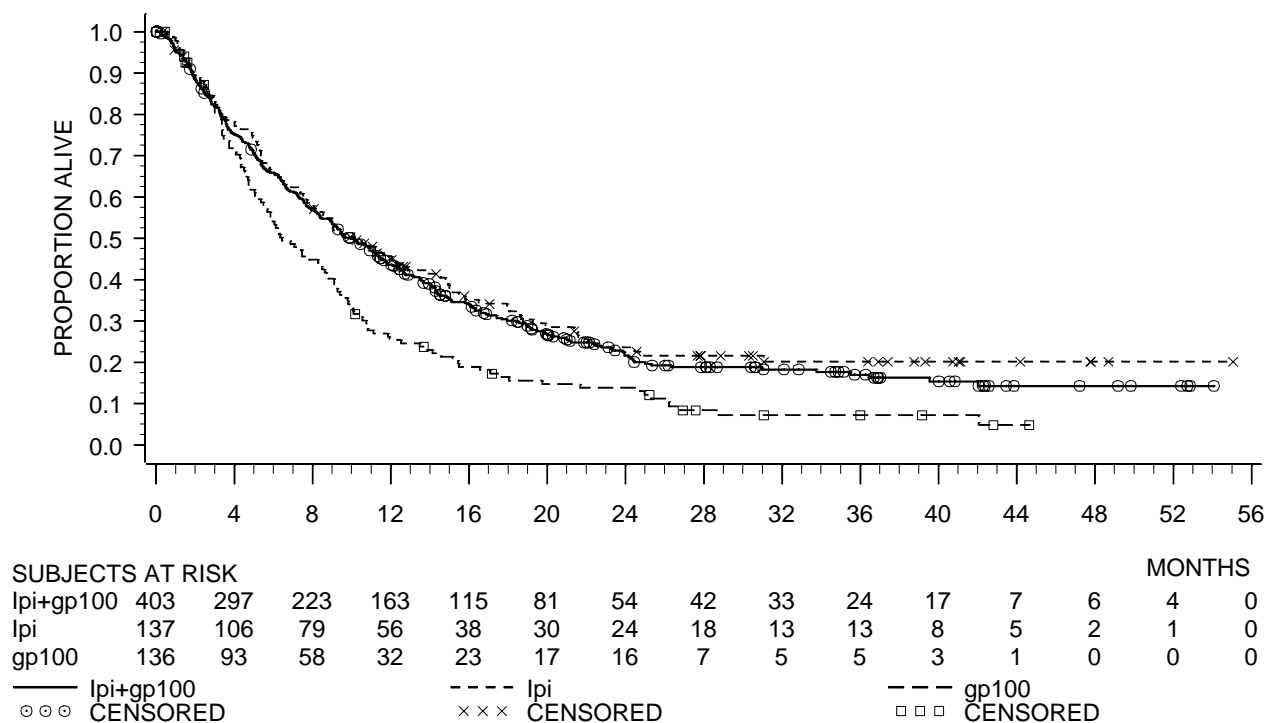
The OS results are shown in Table 3 and [Figure 1](#).

Table 3: Overall Survival Results

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

^a Not adjusted for multiple comparisons.

Figure 1: Overall Survival



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

16 HOW SUPPLIED/STORAGE AND HANDLING

YERVOY is available as follows:

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

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

17 PATIENT COUNSELING INFORMATION

See *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 breast-feed while taking YERVOY.

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MEDICATION GUIDE

YERVOY™ (yur-voi)

(ipilimumab)

Read this Medication Guide before you start receiving YERVOY and before each infusion. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

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
- 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 breast-feeding

Tell your healthcare provider about all the medicines you take, including all 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 your 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

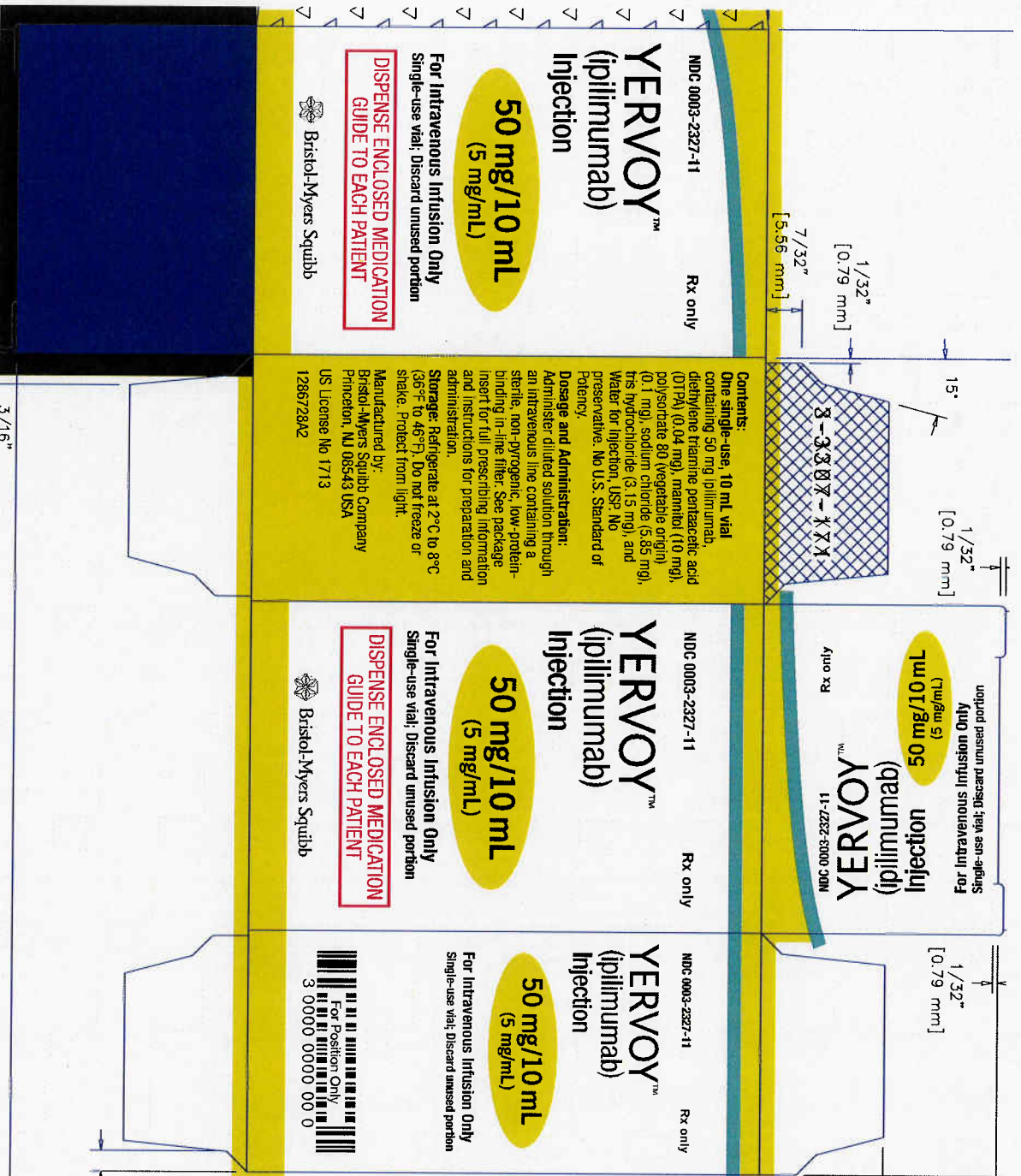
This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

1281558

Issued: March 2011



For Intravenous Infusion Only
 Single-use vial; Discard unused portion



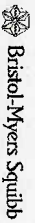
Contents:
 One single-use, 10 mL vial containing 50 mg ipilimumab, diethylene triamine pentaacetic acid (DTPA) (0.04 mg), mannitol (10 mg), polysorbate 80 (vegetable origin) (0.1 mg), sodium chloride (3.85 mg), frs hydrochloride (3.15 mg), and Water for Injection, USP. No preservative. No U.S. Standard of Potency.

Dosage and Administration:
 Administer diluted solution through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter. See package insert for full prescribing information and instructions for preparation and administration.

Storage: Refrigerate at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Protect from light.

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 126672942

For Intravenous Infusion Only
 Single-use vial; Discard unused portion



For Intravenous Infusion Only
 Single-use vial; Discard unused portion

For Position Only
 3 0000 0000 00 0

Discard unused portion
 For intravenous infusion only
 Single-use vial; Discard unused portion

50 mg/10 mL (5 mg/mL)

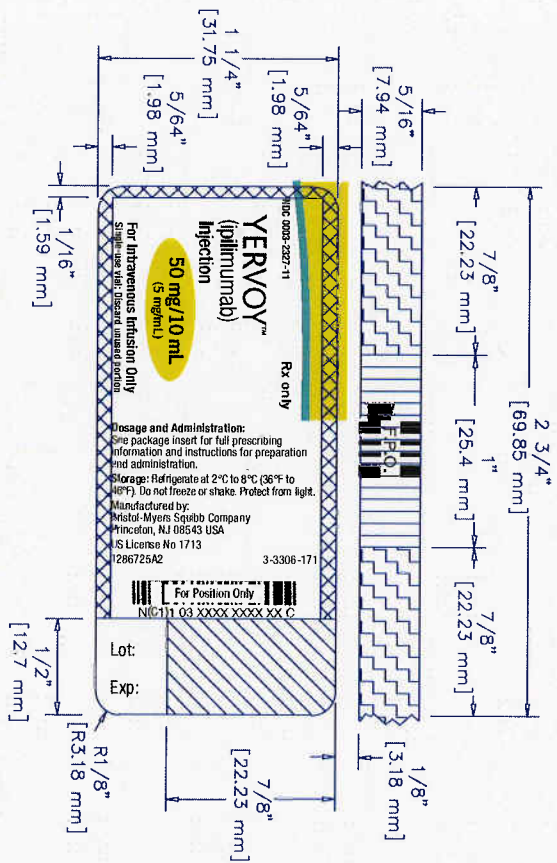
YERVOY™ (ipilimumab) Injection

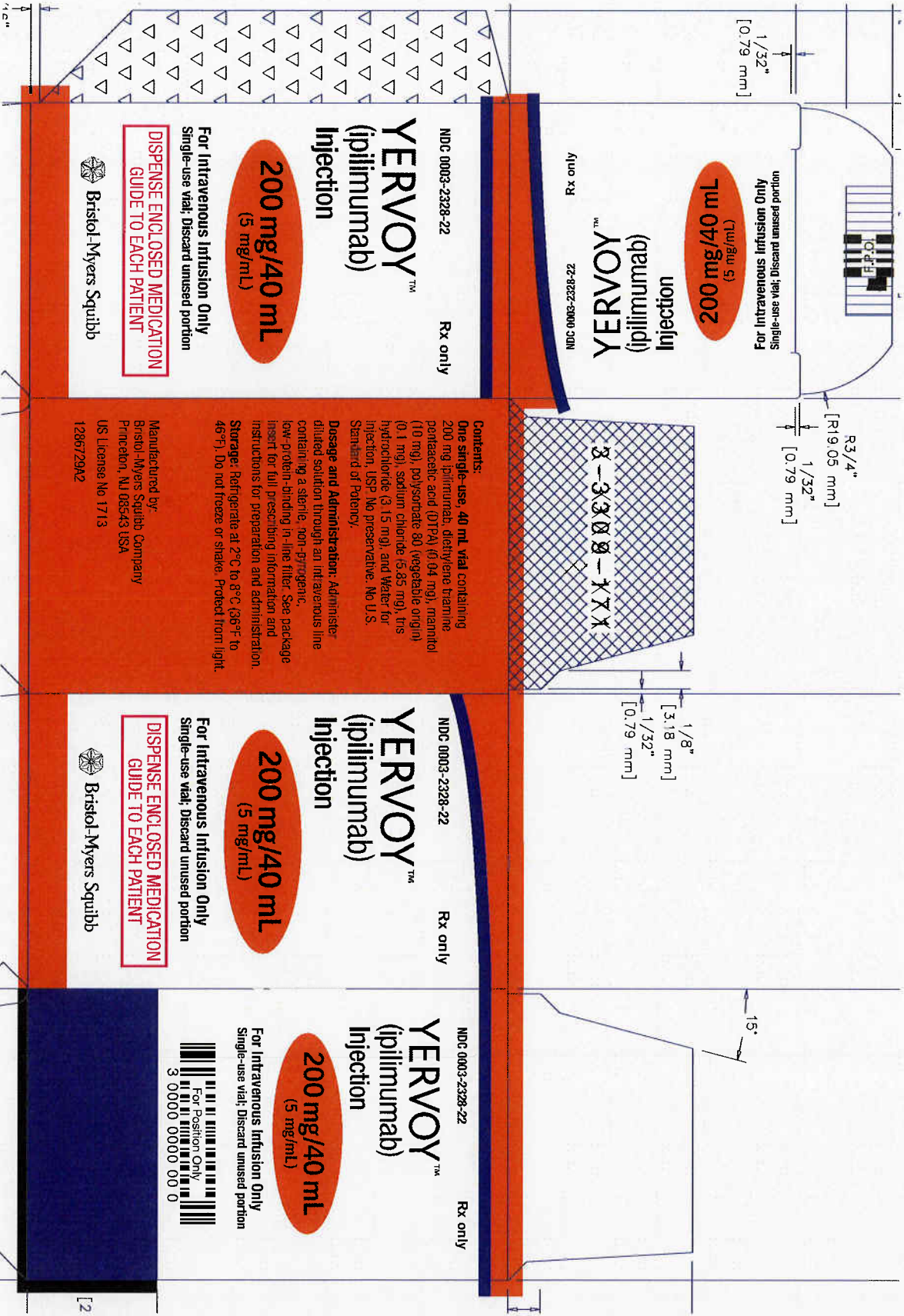
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50 mg/10 mL (5 mg/mL)

YERVOY™ (ipilimumab) Injection

3/16"





$1/32"$
[0.79 mm]

For Intravenous Infusion Only
Single-use vial; Discard unused portion

200 mg/40 mL
(5 mg/mL)

Rx only
NDC 0003-2328-22

YERVOY™
(ipilimumab)
Injection

200 mg/40 mL
(5 mg/mL)

For Intravenous Infusion Only
Single-use vial; Discard unused portion

DISPENSE ENCLOSED MEDICATION
GUIDE TO EACH PATIENT

Bristol-Myers Squibb

$R3/4"$
[19.05 mm]

$1/32"$
[0.79 mm]

3-3300-XXXX

Contents:

One single-use, 40 mL vial containing 200 mg ipilimumab, diethylene diamine pentaacetic acid (DTPA) (0.04 mg), mannitol (10 mg), polysorbate 80 (vegetable origin) (0.1 mg), sodium chloride (5.85 mg), tris hydrochloride (3.15 mg), and Water for Injection, USP. No preservative. No U.S. Standard of Potency.

Dosage and Administration: Administer diluted solution through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter. See package insert for full prescribing information and instructions for preparation and administration. **Storage:** Refrigerate at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Protect from light.

Manufactured by:
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Princeton, NJ 08543 USA
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$1/8"$
[3.18 mm]

$1/32"$
[0.79 mm]

Rx only
NDC 0003-2328-22

YERVOY™
(ipilimumab)
Injection

200 mg/40 mL
(5 mg/mL)

For Intravenous Infusion Only
Single-use vial; Discard unused portion

DISPENSE ENCLOSED MEDICATION
GUIDE TO EACH PATIENT

Bristol-Myers Squibb

15°

Rx only
NDC 0003-2328-22

YERVOY™
(ipilimumab)
Injection

200 mg/40 mL
(5 mg/mL)

For Intravenous Infusion Only
Single-use vial; Discard unused portion

For Position Only
3 0000 0000 00 0

