Initial REMS Approval: 03/2011
Most Recent Modification: 02/2012

BLA 125377 YERVOY (ipilimumab) Injection, for intravenous infusion

Human cytotoxic T-lymphocyte antigen-4 (CTLA-4)-blocking monoclonal Antibody

Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543

Contact:
Phone: 609-897-5854
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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of the YERVOY REMS is to inform healthcare providers about the serious risks associated with YERVOY, including risks of severe and fatal immune-mediated adverse reactions such as fatal immune-mediated enterocolitis (including gastrointestinal perforation), fatal immune-mediated hepatitis (including hepatic failure), fatal immune-mediated toxicities of skin (including toxic epidermal necrolysis), fatal nervous system toxicity, and endocrinopathies, and the management of these reactions.

II. REMS ELEMENTS

A. Communication Plan

Bristol-Myers Squibb Company (Bristol-Myers Squibb) will implement a communication plan to healthcare providers to support implementation of this REMS.

The communication plan will include:

1. At least one week prior to first availability of YERVOY to healthcare providers, and every six months for three years thereafter, Bristol-Myers Squibb will send a communication via direct mail and via electronic delivery to U.S. cancer

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treatment infusion centers, and to the following U.S.-licensed healthcare providers: oncologists, surgical oncologists, oncology nurses, oncology pharmacists, infusion nurses, and cancer treatment infusion nurses. and health-system pharmacists. Recipients will include members of the following organizations:

a. American Society of Clinical Oncology (ASCO)
b. Hematology Oncology Pharmacist Association (HOPA)
c. Infusion Nursing Society (INS)
d. Oncology Nursing Society (ONS)
e. National Comprehensive Cancer Network (NCCN)
f. Society of Surgical Oncologists (SSO)

The following materials will be included in the communications:

a. A *Dear Healthcare Provider Letter* informing healthcare providers about the incidence, type, severity and management of immune-mediated adverse reactions caused by YERVOY
b. The *Immune-Mediated Adverse Reaction Management Guide*
c. The *Patient Wallet Card*
d. The *Nursing Immune-Mediated Adverse Reaction Symptom Checklist*

Communications via mail and electronic delivery will also target all known prescribers and infusion centers that have administered YERVOY.

2. No later than one week after first availability of YERVOY to healthcare providers, and every six months for three years thereafter, Bristol-Myers Squibb will send a communication via electronic delivery to the following non-oncology specialists who may be consulted during the care of patients receiving YERVOY: gastroenterologists, dermatologists, endocrinologists, emergency room physicians, hepatologists, and health-system pharmacists. Recipients will include members of the following organizations:
   a. American Association of Clinical Endocrinology (AACE)
   b. American Academy of Dermatology (AAD)
   c. American Association of Neurology (AAN)
   d. American Association for the Study of Liver Diseases (AASLD)
   e. American College of Emergency Physicians (ACEP)
   f. American Gastroenterological Association (AGA)
   g. American Society of Health-System Pharmacists (ASHP)
   h. Endo Society

The following materials will be included in the communications:

Reference ID: 3088772

a. A *Dear Healthcare Provider Letter* informing healthcare providers about the incidence, type, severity and management of immune-mediated adverse reactions caused by YERVOY
b. The *Immune-Mediated Adverse Reaction Management Guide*

3. No later than 1 week after first availability of YERVOY to healthcare providers, Bristol-Myers Squibb will communicate to the leadership of the headquarters of the above professional societies and the American Academy of Family Physicians (AAFP) and Society of General Internal Medicine (SGIM). This communication will include the communication materials described a-b, above. The letter will request that these societies disseminate this information to their membership.

The *Dear Healthcare Provider Letter*, the *Immune-Mediated Adverse Reaction Management Guide*, the *Patient Wallet Card*, and the *Nursing Immune-Mediated Adverse Reaction Symptom Checklist* are part of the REMS and are appended.

4. Bristol-Myers Squibb will ensure that all communication materials listed above are available in print format and electronic format beginning at least 1 week prior to first availability of YERVOY to healthcare providers and continuing for seven years after initial approval of the REMS via a REMS-dedicated webpage (appended).
5. At least 1 week prior to first availability of YERVOY to healthcare providers and continuing for seven years following approval of the REMS, Bristol-Myers Squibb will ensure that hard copies of the *Nursing Immune-Mediated Adverse Reaction Symptom Checklist*, *Immune-Mediated Adverse Reaction Management Guide* and the *Patient Wallet Card* are available to oncology related specialists.
6. At least 1 week prior to first availability of YERVOY to healthcare providers and continuing for seven years following approval of the REMS, Bristol-Myers Squibb will ensure that hard copies of the *Nursing Immune-Mediated Adverse Reaction Symptom Checklist* and the *Patient Wallet Card* are available to cancer treatment infusion centers.
7. Within 48 hours of receiving notification of a new YERVOY prescriber/purchaser, Bristol-Myers Squibb will attempt to contact the new prescriber/purchaser via phone to communicate the risks of YERVOY and provide printed REMS materials listed in 1. a-d above within 1 week.
8. Beginning with the June 2011 American Society of Clinical Oncology (ASCO) meeting in Chicago, Illinois and continuing for seven years following approval of the REMS, the communication package including all the materials listed in 1. a-d will be available annually at the Bristol-Myers Squibb booth.

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B. Timetable for Submission of Assessments

Bristol-Myers Squibb Company will submit REMS Assessments to FDA 18 months, 3 years, and 7 years from the initial date of the approval of the REMS (March 25, 2011). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for the assessment. Bristol-Myers Squibb will submit each assessment so that it will be received by the FDA on or before the due date.

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Envelope image

Bristol-Myers Squibb
PO Box 1217
Palatine, IL 60078-1217

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IMPORTANT DRUG WARNING

731US11REMS00601 03/11

Approved 930050898 1.0

IMPORTANT DRUG WARNING

Bristol-Myers Squibb

P.O. Box 4500
Princeton, NJ 08543-4500

March 2011

Subject: Risk Evaluation and Mitigation Strategy (REMS) for YERVOY (ipilimumab) on the Risks of and Recommended Management for Severe Immune-mediated Adverse Reactions

Dear Healthcare Provider:

This letter is intended to inform you about the risk evaluation and mitigation strategy (REMS), developed by Bristol-Myers Squibb in collaboration with FDA, that is required to ensure that the benefits of YERVOY outweigh the risks of severe and fatal immune-mediated adverse reactions.

The YERVOY full Prescribing Information includes the following Boxed Warning:

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)]*

This letter is not a comprehensive description of the risks associated with the use of YERVOY. The Boxed Warning summarizes the most common and severe immune-mediated adverse reactions. **Healthcare providers must read the boxed warning and accompanying full Prescribing Information for a complete description of these risks and their management.** You are advised to discuss the risks that may be associated with YERVOY therapy with patients and their caregivers. The YERVOY patient Medication Guide contains information about the known and potential risks of YERVOY.

REMS OVERVIEW

The YERVOY REMS consists of a Communication Plan to inform Healthcare Providers of the serious risks of YERVOY, to facilitate early identification of these risks, and an overview of recommended management of patients with moderate or more severe immune-mediated adverse reactions. Bristol-Myers Squibb will make available this Dear Healthcare Provider Letter and the following communication plan materials in print, electronic and web-based formats:

- *Immune-mediated Adverse Reaction Management Guide*
  - A booklet designed to inform healthcare providers of the signs, symptoms and management of YERVOY immune-mediated adverse reactions
- *Nursing Immune-mediated Adverse Reaction Checklist*
  - A checklist with key questions to ask patients and actions to take when assessing patients for YERVOY immune-mediated adverse reactions
- *Patient Wallet Card*
  - A foldable patient resource containing a list of symptoms associated with YERVOY adverse reactions and contact information for the patient's prescribing healthcare provider

For additional information regarding YERVOY or additional copies of the YERVOY REMS materials you may:

- Call the Bristol-Myers Squibb toll-free medical information line at 1-800-321-1335
- Visit the YERVOY web site at www.YERVOY.com/hcp/rems

REPORTING ADVERSE REACTIONS

Healthcare providers should report all suspected adverse reactions associated with the use of YERVOY. Please contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Sincerely,

John Tsai, MD
Vice President, Head of US Pharmaceuticals Medical
Bristol-Myers Squibb

This letter is required and approved by FDA as part of the YERVOY REMS.

References: YERVOY Full Prescribing Information, 03/11
731US11REMS00101 03/11

YERVOY™ (ipilimumab)

Immune-mediated Adverse Reaction Management Guide

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

This guide is part of an FDA-approved REMS.

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The YERVOY Immune-mediated Adverse Reaction Management Guide

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

The Food and Drug Administration (FDA) approved YERVOY with a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drug outweigh the risks. YERVOY administration can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. Corticosteroid therapy may be required. This guide includes information on the signs and symptoms of YERVOY-induced adverse reactions and presents management guidelines.

HOW TO USE THIS GUIDE

Please read the full Prescribing Information for YERVOY for a comprehensive description of these risks and others.

- Although any organ system can be affected, the following page contains a schematic of the body and the organ systems from which the most common immune-mediated adverse reactions can originate (eg, gastrointestinal, skin)
- Corresponding pages are presented by organ system and provide guidance on how to appropriately manage the associated adverse reactions

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.

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.

For more information, visit www.YERVOY.com/hcp/rems or call 1-855-YERVOY1.

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IMMUNE-MEDIATED ADVERSE REACTIONS

Follow color code to appropriate management guide section.

GASTROINTESTINAL

GO TO PAGE 6

Signs and symptoms such as

- Diarrhea
- Abdominal pain
- Blood or mucus in stool
- Bowel perforation
- Peritoneal signs
- Ileus

LIVER

GO TO PAGE 8

Signs such as

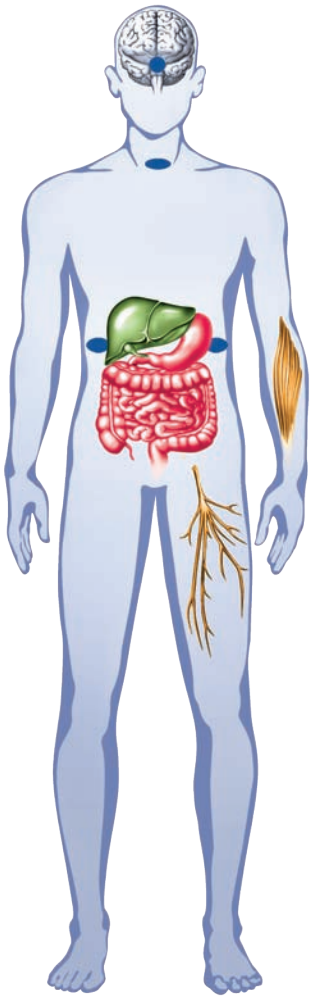
- Abnormal liver function tests (eg, AST, ALT) or total bilirubin

SKIN

GO TO PAGE 10

Symptoms such as

- Pruritus
- Rash



NEUROLOGIC

GO TO PAGE 12

Symptoms such as

- Unilateral or bilateral weakness
- Sensory alterations
- Paresthesia

ENDOCRINE

GO TO PAGE 14

Signs and symptoms such as

- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Unusual bowel habits
- Hypotension
- Abnormal thyroid function tests and/or serum chemistries

OTHER ADVERSE REACTIONS, including ocular manifestations

GO TO PAGE 16

Please see each organ system section for related guidance.

See checklist on the next page.

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Immune-mediated adverse reaction checklist

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 endocrinopathies
- The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY
- It is important to recognize and address symptoms early

This checklist is intended for use prior to dosing each patient and at any follow-up visits with the patient to identify signs and symptoms commonly associated with immune-mediated adverse reactions. This checklist is not meant to be all-inclusive. Please consult the full Prescribing Information and the following pages of the YERVOY Immune-mediated Adverse Reaction Management Guide, visit www.YERVOY.com/hcp/rems, or call 1-855-YERVOY1 for more information.

ASSESS AND ASK THE PATIENT ABOUT THE FOLLOWING SIGNS OR SYMPTOMS

GASTROINTESTINAL

- Any changes in normal bowel habits or changes from baseline (eg, last week, last visit)
  - Diarrhea
  - Abdominal pain
  - Blood or mucus in stool with or without fever
  - Peritoneal signs consistent with bowel perforation
  - Ileus

LIVER

- Elevations in liver function tests
  - AST >2.5 times upper limit of normal (ULN)
  - ALT >2.5 times ULN
  - Total bilirubin >1.5 times ULN

NOTE: Always check lab values prior to each infusion.

SKIN

- Pruritus
- Rash

NEUROLOGIC

- Monitor for symptoms of motor and sensory neuropathy
  - Unilateral or bilateral weakness
  - Sensory alterations
  - Paresthesia

ENDOCRINE

- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Unusual bowel habits
- Hypotension
- Abnormal thyroid function tests and/or serum chemistries

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Immune-mediated adverse reaction checklist (cont'd)

First visit

- Perform baseline assessment
- Check lab values (including liver function and thyroid function tests)
- Educate on importance of vigilance in detecting and prompt reporting of symptoms
- Discuss checklist and key points about immune-mediated adverse reactions
- Provide a copy of Medication Guide and Patient Wallet Card
- Inform patient that it is important to get medical attention for immune-mediated adverse reactions
- Instruct patient not to take any over-the-counter medications or dietary supplements unless approved by his/her treating healthcare provider. Inform patient that these medications or supplements may mask potential serious symptoms that require special treatment

Follow-up visits

- Before each infusion or more frequently if needed, check lab values, including AST, ALT, total bilirubin, and thyroid function tests
- Question patient about immune-mediated symptoms using this checklist
- Reinforce importance of early detection and prompt reporting
- Confirm patient's ability to verbalize important symptoms
- Instruct patient on the appropriate procedure for reporting adverse reactions or seeking medical attention when the office is closed
- Remind patient that symptoms may occur weeks to months after the infusion
- Instruct patient not to take any over-the-counter medications or dietary supplements unless approved by his/her treating healthcare provider. Inform patient that these medications or supplements may mask potential serious symptoms that require special treatment

In the event of an immune-mediated adverse reaction

- Refer to the YERVOY Immune-mediated Adverse Reaction Management Guide and YERVOY full Prescribing Information
- Instruct patient to promptly report any new, persistent, or worsening symptoms to his/her treating healthcare provider
- To report an immune-mediated adverse reaction of YERVOY, please call 1-800-721-5072

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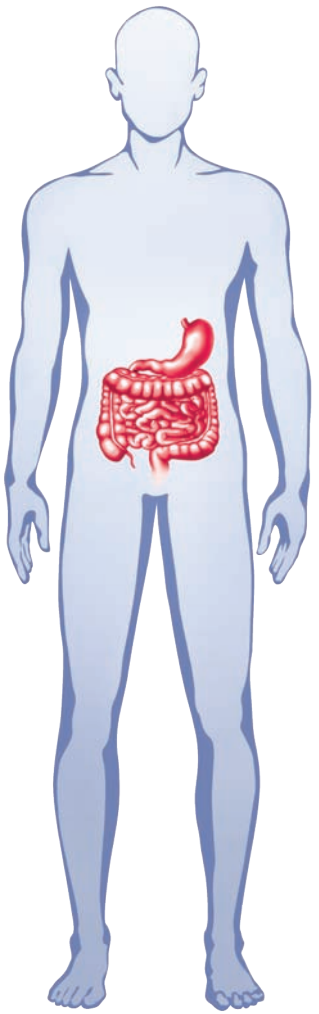

GASTROINTESTINAL

Immune-mediated enterocolitis

- YERVOY (ipilimumab) can result in severe or fatal inflammation of the gastrointestinal tract (with potential risk of bowel perforation) most commonly manifested as diarrhea or colitis
- Advise patients to immediately report changes in bowel movements
- Monitor patients for gastrointestinal signs and symptoms
- Withhold YERVOY treatment for moderate immune-mediated adverse reactions until improvement to mild severity or complete resolution
- Permanently discontinue YERVOY for any of the following
  - Severe or life-threatening enterocolitis
  - 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
- Corticosteroid therapy may be required

GASTROINTESTINAL

Signs and symptoms such as

- Diarrhea
- Abdominal pain
- Blood or mucus in stool with or without fever
- Peritoneal signs consistent with bowel perforation
- Ileus

In symptomatic patients, rule out infectious etiologies, and consider endoscopic evaluation for persistent or severe symptoms.

Unless an alternative etiology has been identified, signs and/or symptoms of enterocolitis should be considered immune-mediated.

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DETERMINE SEVERITY OF ENTEROCOLITIS	MANAGEMENT	FOLLOW UP
Moderate • 4 to 6 stools/day over baseline • Abdominal pain • Blood or mucus in stool	**Withhold YERVOY** • Administer antidiarrheal treatment while etiology is investigated	**Symptoms Resolved** • Resume YERVOY if symptoms have improved to mild severity or resolution **Symptoms Ongoing >1 week** • Start systemic corticosteroids (eg, 0.5 mg/kg/day of prednisone or equivalent) • Continue steroids until improvement to mild severity or resolution; taper steroids as medically appropriate • Resume YERVOY if symptoms have improved to at least mild severity, and steroid dose is 7.5 mg prednisone equivalent or less **IF SYMPTOMS WORSEN TO SEVERE, SEE BELOW**
Severe or Life Threatening • ≥ 7 stools/day over baseline • Peritoneal signs consistent with bowel perforation • Ileus • Fever	**Permanently Discontinue YERVOY** • Rule out bowel perforation; if bowel perforation is present, do not administer corticosteroids • Consider endoscopic evaluation • Administer systemic corticosteroids of 1 to 2 mg/kg/day of prednisone or equivalent	**Symptoms Resolved** • Continue steroids until improvement to mild and taper steroids over 1 month **Symptoms Ongoing** • Patient should be continually evaluated for evidence of gastrointestinal perforation or peritonitis • Consider repeat endoscopy • Consider alternative immunosuppressive therapy

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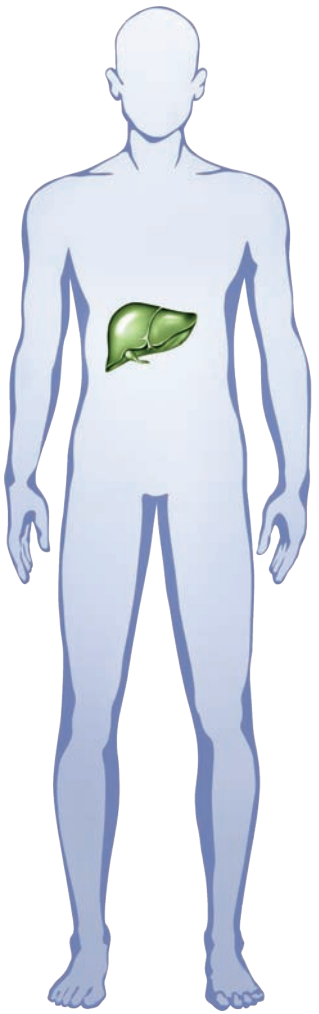

LIVER

Immune-mediated hepatitis

- YERVOY (ipilimumab) can result in severe and fatal inflammation of the liver most commonly manifested as elevation of transaminases and hyperbilirubinemia
- Monitor liver function tests (hepatic transaminase and bilirubin levels) and assess for signs and symptoms of hepatitis before each dose of YERVOY
- Withhold YERVOY dosing in patients with moderate aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations of >2.5 times but ≤5 times upper limit of normal (ULN), or moderate total bilirubin elevation of >1.5 times but ≤3 times ULN
- Permanently discontinue YERVOY for any of the following
  - Severe AST or ALT elevations of >5 times ULN
  - Total bilirubin elevations of >3 times ULN
  - Failure to complete full treatment course within 16 weeks from administration of first dose
- Corticosteroid therapy may be required

LIVER

EVALUATE HEPATIC FUNCTION BEFORE EACH ADMINISTRATION OF YERVOY

Laboratory abnormalities such as

- Elevations in liver function tests (eg, AST, ALT) and/or total bilirubin may occur in the absence of clinical symptoms

In patients with hepatotoxicity, rule out infectious or malignant causes, and increase frequency of liver function test monitoring until resolution.

Unless an alternative etiology has been identified, laboratory abnormalities consistent with hepatitis should be considered immune-mediated.

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DETERMINE SEVERITY OF HEPATITIS	MANAGEMENT	FOLLOW UP
Moderate • AST or ALT >2.5 to ≤5.0 × ULN and/or • Total bilirubin >1.5 to ≤3.0 × ULN	**Withhold YERVOY** • Rule out infectious or malignant causes • Increase frequency of liver function test monitoring until resolution	**Symptoms Resolved** Resume YERVOY if liver function tests are ≤2.5 × ULN or return to baseline and bilirubin level is ≤1.5 × ULN or returns to baseline **Symptoms Ongoing** **IF AST OR ALT CONTINUES TO ELEVATE TO >5.0 × ULN OR TOTAL BILIRUBIN >3.0 × ULN,** **SEE BELOW**
Severe or Life Threatening • AST or ALT >5.0 × ULN and/or • Total bilirubin >3.0 × ULN	**Permanently Discontinue YERVOY** • Rule out infectious or malignant causes • Increase frequency of liver function test monitoring until resolution • Administer systemic corticosteroid of 1 to 2 mg/kg/day of prednisone or equivalent	**Symptoms Resolved** When liver function tests show sustained improvement or return to baseline, initiate corticosteroid tapering and continue to taper over 1 month **Symptoms Ongoing** Consider alternative immunosuppressive therapy

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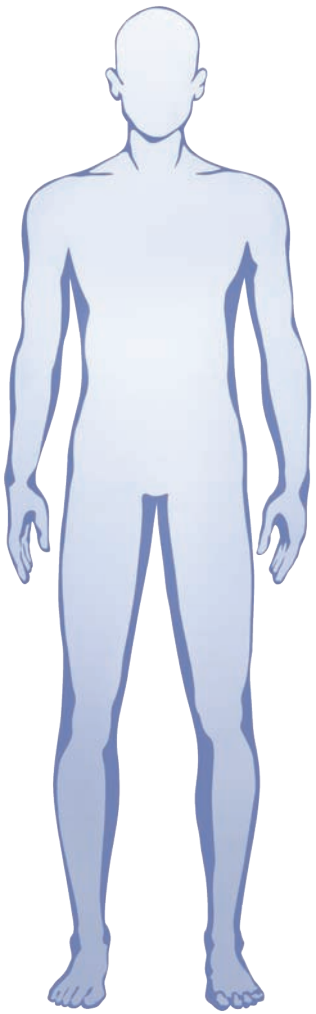

SKIN

Immune-mediated dermatitis

- YERVOY (ipilimumab) can result in severe and fatal inflammation of the skin, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
- Advise patients to report skin-related changes
- Monitor patients for the most common manifestations of immune-mediated dermatitis, such as rash and pruritus
- Withhold YERVOY dosing in patients with moderate to severe signs and symptoms
- Permanently discontinue YERVOY for any of the following
  - Life-threatening immune-mediated dermatitis, such as generalized exfoliative, full thickness dermal ulceration, ulcerative or bullous dermatitis, skin necrosis, SJS, or TEN
  - 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
- Topical and/or systemic corticosteroids may be required

SKIN

Signs and symptoms such as

- Pruritus
- Rash

Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated.

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DETERMINE SEVERITY OF DERMATITIS	MANAGEMENT	FOLLOW UP
Moderate Non-localized rash (diffuse, ≤50% of skin surface)	**Withhold YERVOY** Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week	**Symptoms Resolved** Resume YERVOY if dermatitis resolves or improves to mild (localized) symptoms and systemic steroid dose is 7.5 mg prednisone equivalent or less **Symptoms Ongoing** IF SYMPTOMS WORSEN, SEE BELOW
Severe or Life Threatening Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations	**Permanently Discontinue YERVOY** Administer systemic corticosteroid therapy of 1 to 2 mg/kg/day of prednisone or equivalent	**Symptoms Resolved** When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month

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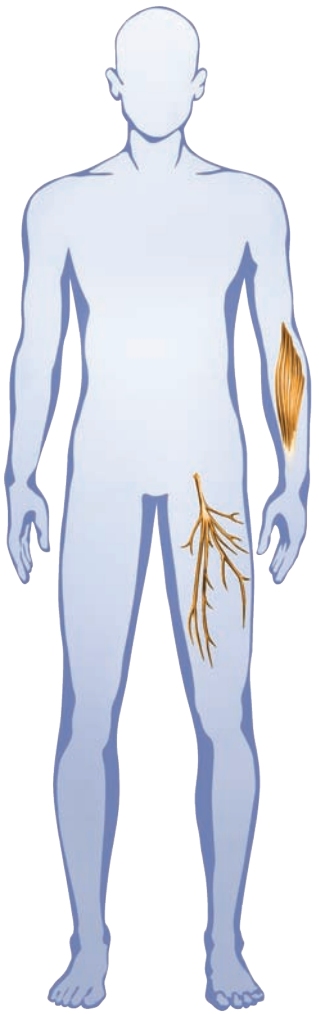

NEUROLOGIC

Immune-mediated neuropathies

- YERVOY (ipilimumab) can cause serious and fatal immune-mediated neurological adverse reactions, including sensory and motor neuropathy, Guillain-Barré syndrome, and myasthenia gravis
- Patients should be advised to immediately report signs or symptoms, such as muscle weakness or sensory alterations
- Monitor patients for signs or symptoms of motor and sensory neuropathy
- Withhold YERVOY in patients with moderate neuropathy (not interfering with daily activities)
- Permanently discontinue YERVOY for any of the following
  - New onset or worsening of severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
  - Failure to complete full treatment course within 16 weeks from administration of first dose
- Corticosteroid therapy may be required

NEUROLOGIC

Signs and symptoms such as

- Unilateral or bilateral weakness
- Sensory alterations
- Paresthesia

Unless an alternative etiology has been identified, signs and symptoms of neuropathy should be considered immune-mediated.

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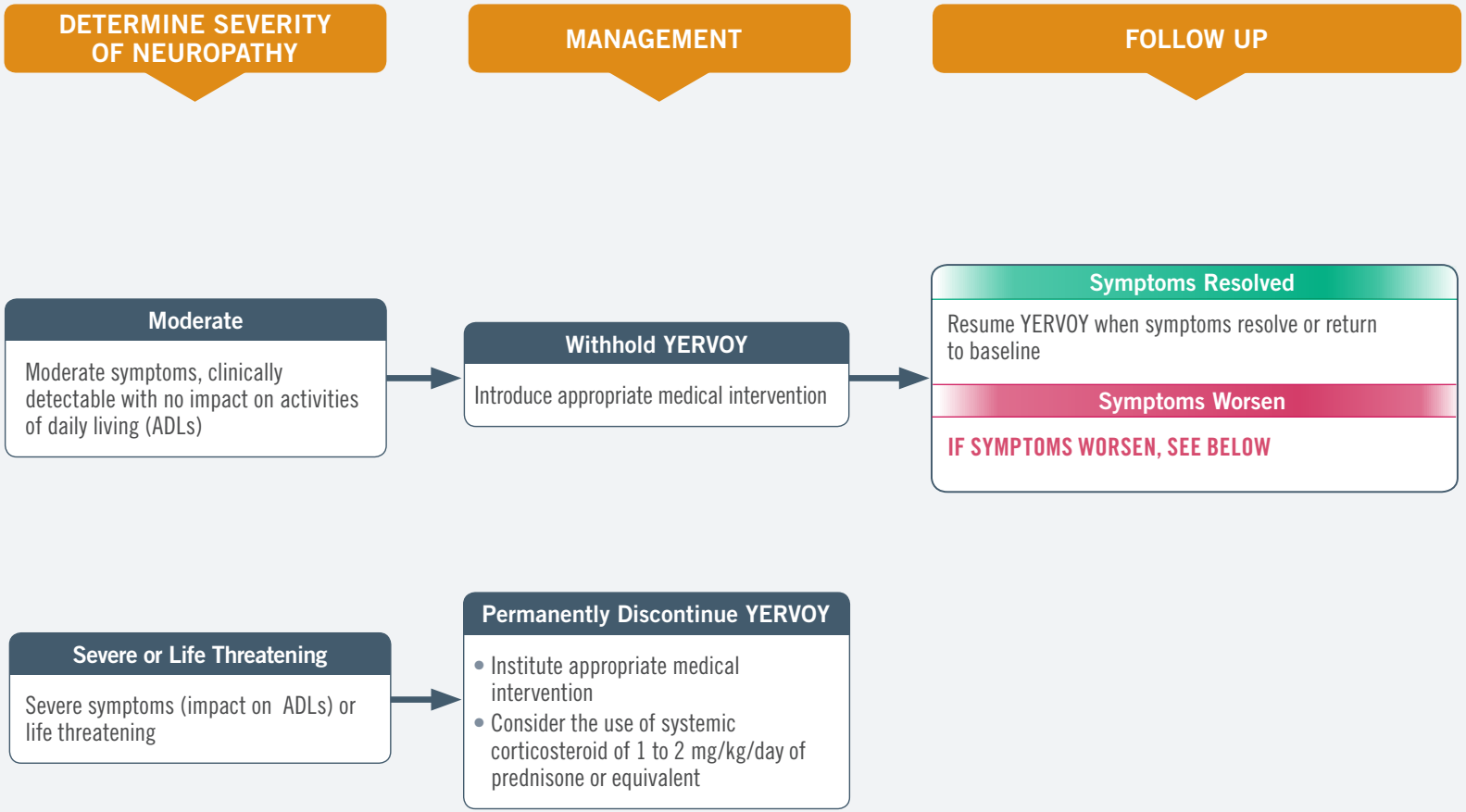

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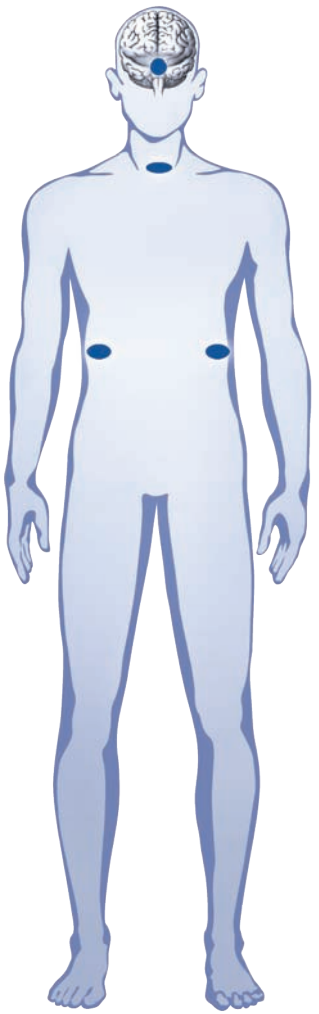

ENDOCRINE

Immune-mediated endocrinopathies

- YERVOY (ipilimumab) can cause severe to life-threatening endocrinopathies, most commonly manifested as hypopituitarism, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism
- Patients should be advised to immediately report symptoms, such as fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension
- Monitor thyroid function tests and clinical chemistries at the start of treatment, before each dose, and as clinically indicated based on signs and symptoms
- Withhold YERVOY treatment for moderate immune-mediated adverse reactions or any symptomatic endocrinopathy until complete resolution or stable on hormone replacement therapy
- Permanently discontinue YERVOY for any of the following
  - 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
- Corticosteroid therapy and/or long-term hormone-replacement therapy may be necessary

ENDOCRINE

Signs and symptoms such as

- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Unusual bowel habits
- Hypotension
- Abnormal thyroid function tests and/or serum chemistries

Patients may present with nonspecific symptoms that may resemble other causes, such as brain metastases or underlying disease.

Unless an alternative etiology has been identified, signs and symptoms of endocrinopathies should be considered immune-mediated.

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DETERMINE SEVERITY OF ENDOCRINOPATHY

Moderate to Life Threatening

- Signs and/or symptoms of dysfunction
- Endocrinopathies requiring hormone replacement or medical intervention
- Adverse reactions requiring hospitalization, urgent medical intervention, or interfering with activities of daily living (including adrenal crisis)

MANAGEMENT

Withhold YERVOY

- Evaluate endocrine function
- Consider radiographic pituitary gland imaging
- Continue to assess as indicated
- Withhold YERVOY in symptomatic patients
- Administer systemic corticosteroid therapy of 1 to 2 mg/kg/day of prednisone or equivalent
- Initiate appropriate hormone-replacement therapy

FOLLOW UP

Symptoms Resolved

Resume YERVOY when

- Patient is stable and symptoms are resolved or return to baseline
- Patient is stable on hormone-replacement therapy (as indicated)
- Patient is receiving ≤7.5 mg prednisone or equivalent per day

Symptoms Worsen

Withhold YERVOY until symptoms are controlled with hormone-replacement therapy

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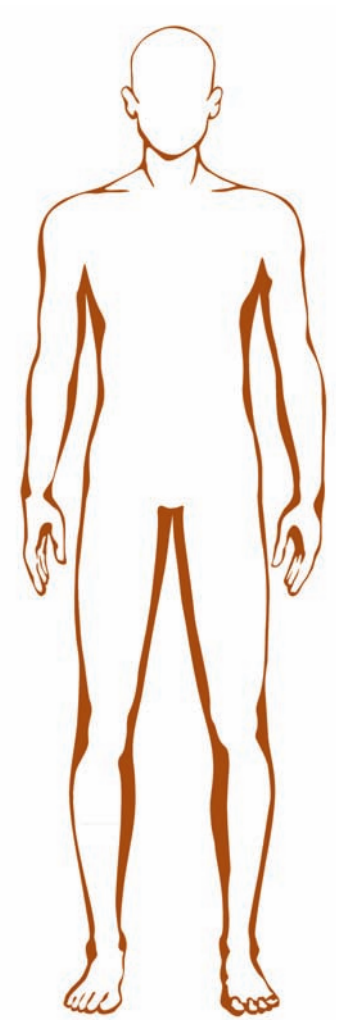

OTHER

Immune-mediated adverse reactions, including ocular manifestations

The following clinically significant immune-mediated adverse reactions have occurred in patients receiving YERVOY

Blood and lymphatic
- hemolytic anemia

Cardiovascular
- angiopathy
- myocarditis
- pericarditis
- temporal arteritis
- vasculitis

Endocrine
- autoimmune thyroiditis

Eye
- blepharitis
- conjunctivitis
- episcleritis
- iritis
- scleritis
- uveitis

Gastrointestinal
- pancreatitis

Infectious
- meningitis

Musculoskeletal
- arthritis
- polymyalgia rheumatica

Renal and urinary
- nephritis

Respiratory
- pneumonitis

Skin
- psoriasis
- leukocytoclastic vasculitis

- Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe immune-mediated adverse reactions
- Permanently discontinue YERVOY for
  - Clinically significant or severe immune-mediated adverse reactions
  - 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
- 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

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YERVOY (ipilimumab)

Immune-mediated Adverse Reaction Management Guide

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YERVOY™ (ipilimumab)
NURSING IMMUNE-MEDIATED ADVERSE REACTION CHECKLIST

Patient name _____ **Date** _____

YERVOY (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma. YERVOY can result in severe and fatal immune-mediated adverse reactions (**please see YERVOY full Prescribing Information for additional information**). The majority of immune-mediated reactions occurred during treatment; however, a few occurred weeks to months after discontinuation of YERVOY. It is important to recognize and address symptoms early. This checklist is intended for use prior to dosing each patient and at any follow-up visits or calls with the patient to identify signs and symptoms associated with YERVOY immune-mediated adverse reactions. This checklist is not meant to be all-inclusive.

- **ASK THE PATIENT ABOUT THE FOLLOWING SIGNS OR SYMPTOMS**
- **CALL THE PRESCRIBER BEFORE GIVING YERVOY IF THE PATIENT ANSWERS YES TO ANY OF THESE QUESTIONS**

GENERAL	Response		Notes
Are you unable to perform your normal activities?	Yes ☐	No ☐	
Are you having difficulty sleeping?	Yes ☐	No ☐	
Do you have a fever?	Yes ☐	No ☐	
Are you having headaches?	Yes ☐	No ☐	
Have you felt dizzy or light-headed?	Yes ☐	No ☐	
Have you noticed changes in your vision? If yes, how?	Yes ☐	No ☐	
Are you having problems with your eyes?	Yes ☐	No ☐	
Has your appetite changed? If yes, how?	Yes ☐	No ☐	
Have you had any changes in your libido?	Yes ☐	No ☐	
Are you having difficulty breathing?	Yes ☐	No ☐	
Have you started taking any new medications (prescription, nonprescription, or herbal)? If yes, which and when?	Yes ☐	No ☐	
GASTROINTESTINAL			
Are you nauseous and/or vomiting?	Yes ☐	No ☐	
How many bowel movements are you having each day?			
– Is this different than normal? If yes, how?	Yes ☐	No ☐	
– Are your stools loose or watery, or do they have a foul smell?	Yes ☐	No ☐	
– Are you doing anything to manage it? If yes, what?	Yes ☐	No ☐	
Are you having painful bowel movements?	Yes ☐	No ☐	
Are you having cramping?	Yes ☐	No ☐	
Are you having pain in your belly? If yes, where?	Yes ☐	No ☐	
Have you seen blood or mucus in your stools?	Yes ☐	No ☐	
SKIN			
Does your skin itch?	Yes ☐	No ☐	
– If yes, is it keeping you up at night?	Yes ☐	No ☐	
Do you have a rash? If yes, where?	Yes ☐	No ☐	
– If yes, what are you using for it?			
Have you noticed that your skin is turning yellow?	Yes ☐	No ☐	
NEUROLOGIC			
Are you having weakness in your hands or legs?	Yes ☐	No ☐	
Are you having trouble gripping things?	Yes ☐	No ☐	
Have you noticed that you are dropping things?	Yes ☐	No ☐	
Are you having difficulty walking or are you unsteady?	Yes ☐	No ☐	
Are you having difficulty getting up from a chair?	Yes ☐	No ☐	
Are you having numbness or tingling in your hands or feet?	Yes ☐	No ☐	
Are you having trouble buttoning your shirt or pants?	Yes ☐	No ☐	
Are you having trouble picking things up?	Yes ☐	No ☐	

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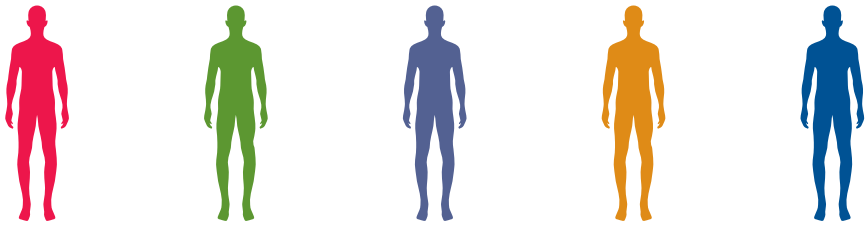
Please see full Prescribing Information for YERVOY, visit www.YERVOY.com/hcp/rems, or call 1-855-YERVOY1 for more information. This checklist is part of an FDA-approved REMS.

YERVOY™
(ipilimumab)

Patient Wallet Card



YERVOY™ Patient Wallet Card

YERVOY (ipilimumab) can cause serious side effects in many parts of your body that can lead to death and need to be addressed right away by your treating healthcare provider

Call your treating healthcare provider right away if you have any of these symptoms

Symptoms that may appear mild can quickly worsen if left untreated

Symptoms may be delayed and may occur weeks to months after your last infusion

Do not feel embarrassed or that you are bothering your healthcare provider

STOMACH AND BOWEL

- Diarrhea (loose stools) or more bowel movements than usual
- Blood in stools or dark, tarry, sticky stools
- Stomach pain (abdominal pain) or tenderness

EYES

- Blurry vision, double vision, or other vision problems
- Eye pain or redness

SKIN

- Skin rash with or without itching
- Mouth sores
- Blisters and/or peeling

GENERAL

- Headache
- Feeling tired
- Nausea or vomiting
- Dizziness or fainting
- Yellowing of your skin or the whites of your eyes
- Dark urine
- Bleeding or bruising more easily than normal
- Weakness of legs, arms, or face
- Numbness or tingling in hands or feet
- Changes in behavior, such as less sex drive, being irritable, or forgetful
- Fever

IMPORTANT
Reminders for patients

- **Do not treat any of these symptoms with over-the-counter medications, dietary supplements, or prescription medications without the approval of your treating healthcare provider**
- **Take this card with you if you go to the Emergency Room or see any doctor other than your treating healthcare provider**
- **Be sure to tell all healthcare providers you see that you are being treated with YERVOY (ipilimumab) and SHOW THEM THIS CARD**

YERVOY can cause serious side effects in many parts of your body. These side effects are most likely to begin during the treatment period, however side effects can show up months after your last infusion. These side effects may require special treatment.

If you experience any symptoms listed on this card, please notify your treating healthcare provider immediately. Even seemingly mild symptoms can lead to severe or even life-threatening conditions if not addressed. Please share this card with all of your healthcare providers and tell them you are being treated with YERVOY.

Please read the YERVOY Medication Guide and talk to your healthcare provider.

For more information, visit www.YERVOY.com or call 1-800-321-1335.

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MY TREATING HEALTHCARE PROVIDER CONTACT INFORMATION

Name of treating healthcare provider

Office phone

After-hours phone

My name and phone

Reference ID: 3088772

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For Healthcare Providers
IMPORTANT INFORMATION

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.

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.

Please see full Prescribing Information and YERVOY Immune-mediated Adverse Reaction Management Guide, visit www.YERVOY.com/hcp/rems, or call 1-855-YERVOY1 for more information.

This wallet card is approved by the U.S. Food and Drug Administration

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REMS
http://www.yervoy.com/hcp/rems.aspx

Important Safety Information | U.S. Full Prescribing Information | Medication Guide

YERVOY (IPILIMUMAB): SERIOUS AND FATAL IMMUNE-MEDIATED ADVERSE REACTIONS

The YERVOY Risk Evaluation and Mitigation Strategy (REMS) is designed to inform healthcare providers about the risk of serious immune-mediated adverse reactions caused by YERVOY. In order for Bristol-Myers Squibb to communicate certain risks about YERVOY, Bristol-Myers Squibb has worked with the FDA to develop materials to communicate the risks of severe and fatal:

- Immune-mediated enterocolitis (including gastrointestinal perforation)
- Immune-mediated hepatitis (including hepatic failure)
- Immune-mediated dermatitis (including toxic epidermal necrolysis)
- Immune-mediated neuropathies
- Immune-mediated endocrinopathies

To learn more about the serious immune-mediated adverse reactions caused by YERVOY, read the Important Safety Information provided in this link, including the Medication Guide, and discuss it with your patients.

Downloadable REMS Materials

DEAR HEALTHCARE PROVIDER LETTER

A communication to healthcare providers conveying Important Safety Information for YERVOY, including the risks of serious immune-mediated adverse reactions.

DOWNLOAD 721k

YERVOY IMMUNE-MEDIATED ADVERSE REACTION MANAGEMENT GUIDE

A booklet designed to inform healthcare providers of the signs, symptoms and management of YERVOY immune-mediated adverse reactions.

DOWNLOAD 4.09MB

NURSING IMMUNE-MEDIATED ADVERSE REACTION CHECKLIST

Checklist with key questions to ask patients and actions to take when assessing patients for YERVOY immune-mediated adverse reactions.

DOWNLOAD 456k

PATIENT WALLET CARD

A foldable patient resource containing a list of symptoms associated with YERVOY immune-mediated adverse reactions and contact information for the patient's treating healthcare provider.

DOWNLOAD 253k

DOWNLOAD ALL MATERIALS 1.9 MB

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/s/

JEFFERY L SUMMERS
02/16/2012