

# 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.

Approved 930050989 1.0

## 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/remis](http://www.YERVOY.com/hcp/remis) or call 1-855-YERVOY1.

# 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

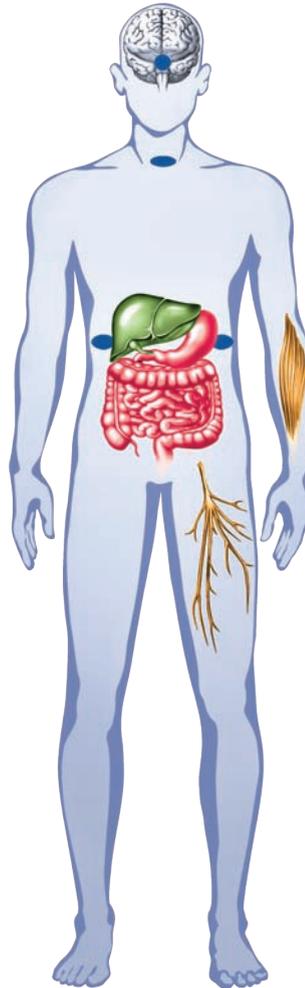
- Abnormal liver function tests (eg, AST, ALT) or total bilirubin

## 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.

# 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/remis](http://www.YERVOY.com/hcp/remis), 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

## 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

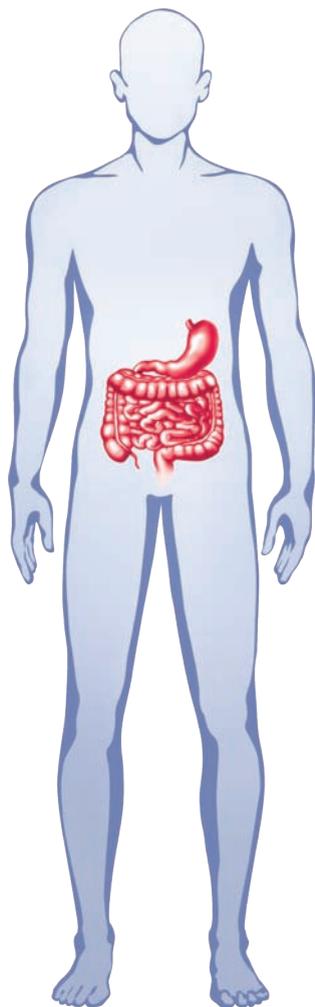
### ▶ Follow-up visits

- 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

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### ▶ 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



# 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.**



## DETERMINE SEVERITY OF ENTEROCOLITIS

## MANAGEMENT

## FOLLOW UP

Gastrointestinal

### 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

- $\geq 7$  stools/day over baseline
- Peritoneal signs consistent with bowel perforation
- Ileus
- Fever

### Permanently Discontinue YERVOY

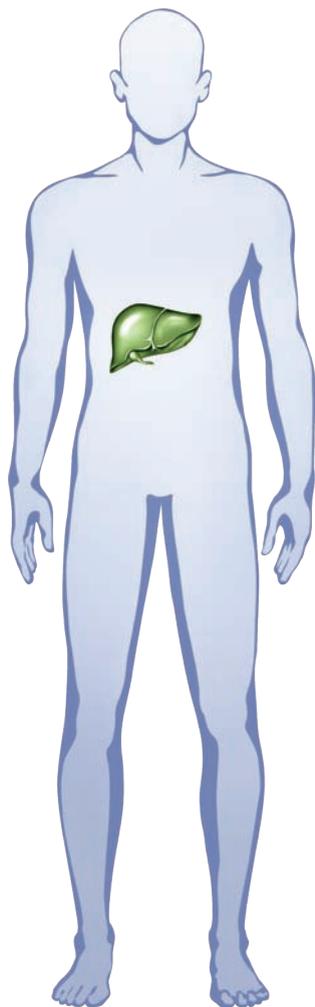
- Rule out bowel perforation; if bowel perforation is present, do not administer corticosteroids
- Consider endoscopic evaluation
- Administer systemic corticosteroids of 1 to 2 mg/kg/day of prednisone or equivalent

### 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



# 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  $\leq 5$  times upper limit of normal (ULN), or moderate total bilirubin elevation of  $>1.5$  times but  $\leq 3$  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.**

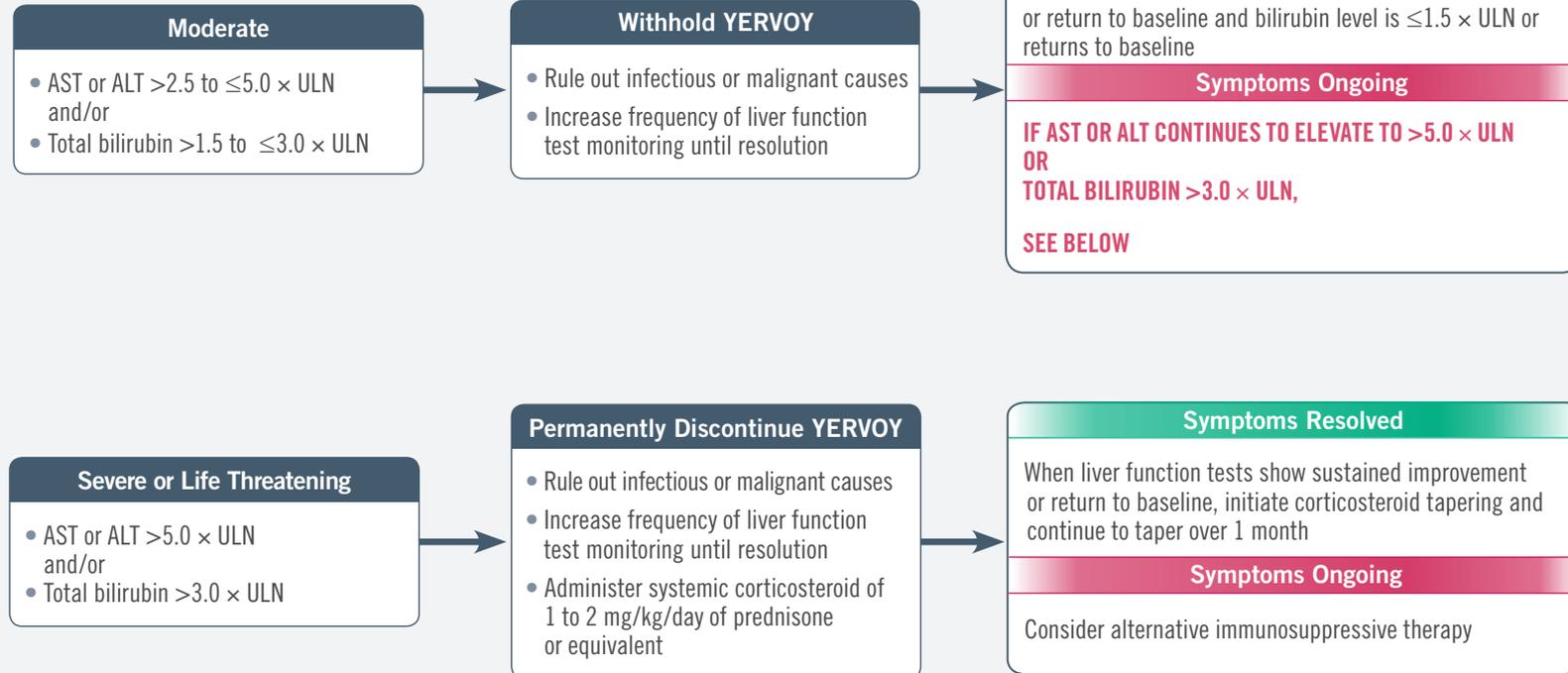
**Unless an alternative etiology has been identified, laboratory abnormalities consistent with hepatitis should be considered immune-mediated.**



## DETERMINE SEVERITY OF HEPATITIS

## MANAGEMENT

## FOLLOW UP





## 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.**



### DETERMINE SEVERITY OF DERMATITIS

### MANAGEMENT

### FOLLOW UP

**Moderate**  
Non-localized rash (diffuse,  $\leq 50\%$  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

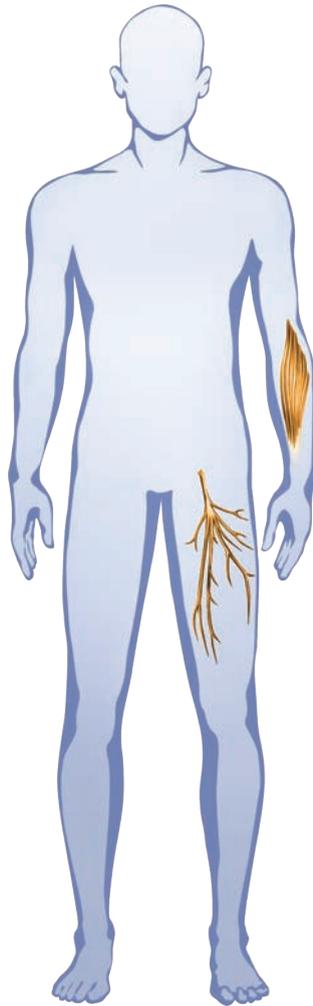
**Symptoms Ongoing**  
**IF SYMPTOMS WORSEN, SEE BELOW**

**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





## 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.**



## DETERMINE SEVERITY OF NEUROPATHY

## MANAGEMENT

## FOLLOW UP

### Moderate

Moderate symptoms, clinically detectable with no impact on activities of daily living (ADLs)

### Withhold YERVOY

Introduce appropriate medical intervention

### Symptoms Resolved

Resume YERVOY when symptoms resolve or return to baseline

### Symptoms Worsen

**IF SYMPTOMS WORSEN, SEE BELOW**

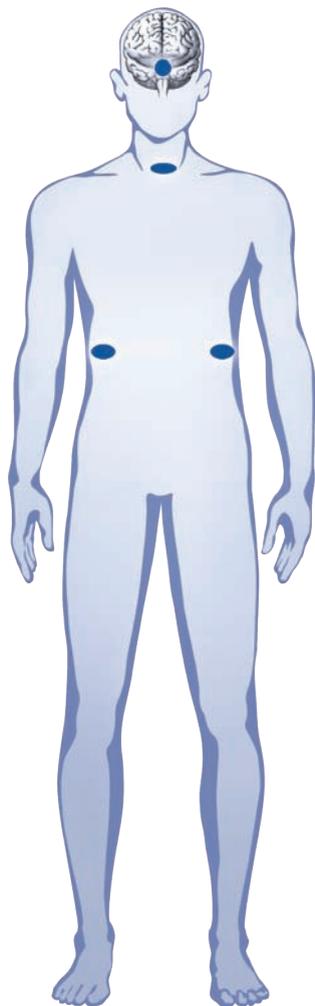
### Severe or Life Threatening

Severe symptoms (impact on ADLs) or life threatening

### Permanently Discontinue YERVOY

- Institute appropriate medical intervention
- Consider the use of systemic corticosteroid of 1 to 2 mg/kg/day of prednisone or equivalent

Neurologic



# 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

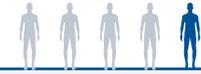
### ENDOCRINE

#### 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.**



## DETERMINE SEVERITY OF ENDOCRINOPATHY

## MANAGEMENT

## FOLLOW UP

### 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)

### 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

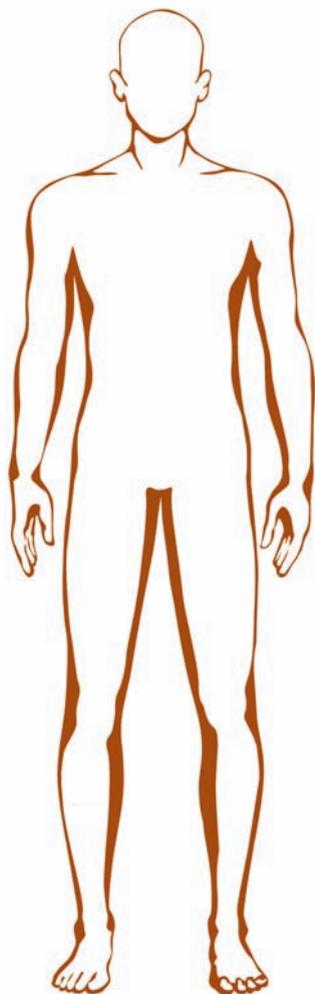
### Symptoms Resolved

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  $\leq 7.5$  mg prednisone or equivalent per day

### Symptoms Worsen

Withhold YERVOY until symptoms are controlled with hormone-replacement therapy



## 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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