BAVENCIO® avelumab Injection 20 mg/mL

Dosing and Treatment Management Guide

INDICATIONS

Metastatic Merkel cell carcinoma (MCC)

- BAVENCIO® (avelumab) is indicated for the treatment of adults and pediatric patients 12 years and older with metastatic MCC. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials

First-line maintenance treatment of urothelial carcinoma (UC)

- BAVENCIO is indicated for the maintenance treatment of patients with locally advanced or metastatic UC that has not progressed with first-line platinum-containing chemotherapy

Previously treated urothelial carcinoma (UC)

- BAVENCIO is indicated for the treatment of patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

SELECTED SAFETY INFORMATION

BAVENCIO can cause **severe and fatal immune-mediated adverse reactions** in any organ system or tissue and at any time after starting treatment with a PD-1/PD-L1 blocking antibody, including after discontinuation of treatment.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

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BAVENCIO® (avelumab) dosing

Recommended dosage

800 mg IV infusion over 60 minutes every 2 weeks

- BAVENCIO is administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity

Premedication

- Premedicate patients with an antihistamine and with acetaminophen prior to the first 4 infusions of BAVENCIO
- Premedication should be administered for subsequent BAVENCIO doses based upon clinical judgment and presence/severity of prior infusion reactions

SELECTED SAFETY INFORMATION

No dose reduction for BAVENCIO is recommended. For immune-mediated adverse reactions, withhold or permanently discontinue BAVENCIO depending on severity. In general, withhold BAVENCIO for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue BAVENCIO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids. In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic corticosteroids (eg, endocrinopathies and dermatologic reactions) are discussed in subsequent sections.

BAVENCIO can cause **immune-mediated pneumonitis**. Withhold BAVENCIO for Grade 2, and permanently discontinue for Grade 3 or Grade 4 pneumonitis. Immune-mediated pneumonitis occurred in 1.2% (21/1738) of patients, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%), and Grade 2 (0.6%) adverse reactions. Systemic corticosteroids were required in all (21/21) patients with pneumonitis.

Preparation and administration

Preparation

- Visually inspect vial for particulate matter and discoloration. BAVENCIO is a clear, colorless to slightly yellow solution. Discard vial if the solution is cloudy, discolored, or contains particulate matter
- Withdraw the required volume of BAVENCIO from the vial(s) and inject it into a 250 mL infusion bag containing either 0.9% Sodium Chloride Injection or 0.45% Sodium Chloride Injection
- Gently invert the bag to mix the diluted solution, avoid foaming or excessive shearing
- Inspect the solution to ensure it is clear, colorless, and free of visible particles
- Discard any partially used or empty vials

Injection: 200 mg/10 mL (20 mg/mL) solution for infusion in a single-dose vial.

Storage of diluted solution

Protect from light.

- Store diluted BAVENCIO solution
  - At room temperature up to 77°F (25°C) for no more than 4 hours from the time of dilution, or
  - Under refrigeration at 36°F to 46°F (2°C to 8°C) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration

Do not freeze or shake the diluted solution.

Administration

- Administer the diluted solution over 60 minutes through an intravenous line containing a sterile, nonpyrogenic, low protein binding in-line filter (pore size of 0.2 micron)
- Do not coadminister other drugs through the same intravenous line

SELECTED SAFETY INFORMATION

BAVENCIO can cause **immune-mediated colitis**. The primary component of immune-mediated colitis consisted of diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade 4 colitis. Immune-mediated colitis occurred in 1.5% (26/1738) of patients, including Grade 3 (0.4%) and Grade 2 (0.7%) adverse reactions. Systemic corticosteroids were required in all (26/26) patients with colitis.

BAVENCIO can cause **hepatotoxicity and immune-mediated hepatitis**. Withhold or permanently discontinue BAVENCIO based on tumor involvement of the liver and severity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin elevation. Immune-mediated hepatitis occurred with BAVENCIO as a single agent in 0.9% (16/1738) of patients, including fatal (0.1%), Grade 3 (0.6%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in all (16/16) patients with hepatitis.

BAVENCIO can cause primary or secondary **immune-mediated adrenal insufficiency**. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated adrenal insufficiency occurred in 0.5% (8/1738) of patients, including Grade 3 (0.1%) and Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in all (8/8) patients with adrenal insufficiency.

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In metastatic MCC

Adverse reactions in ≥10% of patients receiving BAVENCIO® (avelumab)

Adverse Reactions (≥10%)	BAVENCIO (N=88)	
	All Grades %	Grade 3-4 %
General Disorders		
Fatigue[a]	50	2
Infusion-related reaction[b]	22	0
Peripheral edema[c]	20	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[d]	32	2
Arthralgia	16	1
Gastrointestinal Disorders		
Diarrhea	23	0
Nausea	22	0
Constipation	17	1
Abdominal pain[e]	16	2
Vomiting	13	0
Skin and Subcutaneous Tissue Disorders		
Rash[f]	22	0
Pruritus[g]	10	0
Metabolism and Nutrition Disorders		
Decreased appetite	20	2
Decreased weight	15	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough	18	0
Dyspnea[h]	11	1
Nervous System Disorders		
Dizziness	14	0
Headache	10	0
Vascular Disorders		
Hypertension	13	6

[a] Fatigue is a composite term that includes fatigue and asthenia.
[b] Infusion-related reaction is a composite term that includes drug hypersensitivity, hypersensitivity, chills, pyrexia, back pain, and hypotension.
[c] Peripheral edema is a composite term that includes peripheral edema and peripheral swelling.
[d] Musculoskeletal pain is a composite term that includes back pain, myalgia, neck pain, pain in extremity.
[e] Abdominal pain is a composite term that includes abdominal pain and abdominal pain upper.
[f] Rash is a composite term that includes rash maculo-papular, erythema, and dermatitis bullous.
[g] Pruritus is a composite term that includes pruritus and pruritus generalized.
[h] Dyspnea is a composite term that includes dyspnea and dyspnea exertional.

SELECTED SAFETY INFORMATION

BAVENCIO can cause **immune-mediated hypophysitis**. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated pituitary disorders occurred in 0.1% (1/1738) of patients, which was a Grade 2 (0.1%) adverse reaction.

In locally advanced or metastatic UC as first-line maintenance treatment

Adverse reactions (≥10%) of patients receiving BAVENCIO + best supportive care (BSC)

Adverse Reactions (≥10%)	BAVENCIO + BSC (N=344)		BSC (N=345)	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
General Disorders and Administration Site Conditions				
Fatigue[a]	35	1.7	13	1.7
Pyrexia	15	0.3	3.5	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[b]	24	1.2	15	2.6
Arthralgia	16	0.6	6	0
Skin and Subcutaneous Tissue Disorders				
Rash[c]	20	1.2	2.3	0
Pruritus	17	0.3	1.7	0
Infections and Infestations				
Urinary tract infection[d]	20	6	11	3.8
Gastrointestinal Disorders				
Diarrhea	17	0.6	4.9	0.3
Constipation	16	0.6	9.0	0
Nausea	16	0.3	6	0.6
Vomiting	13	1.2	3.5	0.6
Respiratory, Thoracic and Mediastinal Disorders				
Cough[e]	14	0.3	4.6	0
Metabolism and Nutrition Disorders				
Decreased appetite	14	0.3	7	0.6
Endocrine disorders				
Hypothyroidism	12	0.3	0.6	0
Injury, Poisoning and Procedural Complications				
Infusion-related reaction	10	0.9	0	0

[a] Fatigue is a composite term that includes fatigue, asthenia, and malaise.
[b] Musculoskeletal pain is a composite term that includes musculoskeletal pain, back pain, myalgia, and neck pain.
[c] Rash is a composite term that includes rash, rash maculo-papular, erythema, dermatitis acneiform, eczema, erythema multiforme, rash erythematous, rash macular, rash papular, rash pruritic, drug eruption, and lichen planus.
[d] Urinary tract infection is a composite term that includes urinary tract infection, urosepsis, cystitis, kidney infection, pyuria, pyelonephritis, bacteriuria, pyelonephritis acute, urinary tract infection bacterial, and Escherichia urinary tract infection.
[e] Cough is a composite term that includes cough and productive cough.

In previously treated locally advanced or metastatic UC

The most common adverse reactions (≥20%) in patients were fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection.

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Important information on selected adverse reactions with BAVENCIO® (avelumab)

- The data below and on the following pages related to immune-mediated adverse reactions and infusion-related reactions are based on data from over 1700 patients treated with BAVENCIO 10 mg/kg across multiple tumor types, the majority of whom were treated with BAVENCIO monotherapy
- This included 88 patients with metastatic MCC (JAVELIN Merkel 200 Trial) and 242 patients with locally advanced and metastatic UC (JAVELIN Solid Tumor Trial)

Severe and fatal immune-mediated adverse reactions

- BAVENCIO is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions
- Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions
- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and at any time after starting treatment with a PD-1/PD-L1 blocking antibody
- While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, they can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies

Monitor and Assess

- Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1blocking antibodies
- Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions
- Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment
- In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate

General Dose Modifications

- No dose reduction for BAVENCIO is recommended
- In general, withhold BAVENCIO for severe (Grade 3) immune-mediated adverse reactions
- Permanently discontinue BAVENCIO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids
  - Dosage modifications for BAVENCIO for adverse reactions that require management different from these general guidelines are summarized on the following pages

General Corticosteroid Management

- In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less
  - Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month
  - Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy
  - Toxicity management guidelines for adverse reactions that do not necessarily require systemic corticosteroids (eg, endocrinopathies and dermatologic reactions) are discussed on the following pages

SELECTED SAFETY INFORMATION

BAVENCIO can cause **immune-mediated thyroid disorders**. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Thyroiditis occurred in 0.2% (4/1738) of patients, including Grade 2 (0.1%) adverse reactions. Hyperthyroidism occurred in 0.4% (7/1738) of patients, including Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in 29% (2/7) of patients with hyperthyroidism. Hypothyroidism occurred in 5% (90/1738) of patients, including Grade 3 (0.2%) and Grade 2 (3.7%) adverse reactions. Systemic corticosteroids were required in 7% (6/90) of patients with hypothyroidism.

Immune-mediated pneumonitis

Clinical trial experience

- BAVENCIO® (avelumab) can cause immune-mediated pneumonitis
- Across clinical studies,* immune-mediated pneumonitis occurred in 1.2% (21/1738) of patients receiving BAVENCIO, including:
  - Fatal (0.1%) adverse reactions
  - Grade 4 (0.1%) adverse reactions
  - Grade 3 (0.3%) adverse reactions
  - Grade 2 (0.6%) adverse reactions
- Pneumonitis led to permanent discontinuation of BAVENCIO in 0.3% and withholding of BAVENCIO in 0.3% of patients
- Systemic corticosteroids were required in all (21/21) patients with pneumonitis
- Pneumonitis resolved in 57% (12/21) of the patients
- Of the 5 patients in whom BAVENCIO was withheld for pneumonitis, 5 reinitiated treatment with BAVENCIO after symptom improvement
  - Of these, none had recurrence of pneumonitis
- With other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation

MONITOR

Monitor patients for signs and symptoms of pneumonitis, including		
Cough	Shortness of breath	Chest pain

ASSESS

Assess the severity of the adverse reaction[2]			
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (eg, tracheotomy or intubation)

ADL, activities of daily living.

MODIFY

Modify treatment based on severity	
Withhold†	**Permanently discontinue**
For Grade 2	For Grade 3 or 4

- In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

†Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating corticosteroids.

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Immune-mediated colitis

Clinical trial experience

- BAVENCIO can cause immune-mediated colitis
- Across clinical studies,* immune-mediated colitis occurred in 1.5% (26/1738) of patients receiving BAVENCIO, including:
  - Grade 3 (0.4%) adverse reactions
  - Grade 2 (0.7%) adverse reactions
- Colitis led to permanent discontinuation of BAVENCIO in 0.5% and withholding of BAVENCIO in 0.5% of patients
- Systemic corticosteroids were required in all (26/26) patients with colitis
- Colitis resolved in 69% (18/26) of the patients
- Of the 8 patients in whom BAVENCIO was withheld for colitis, 5 reinitiated treatment with BAVENCIO after symptom improvement
  - Of these, 40% had recurrence of colitis

MONITOR

Monitor patients for signs and symptoms of colitis, including

Diarrhea	Stools that are black, tarry, sticky, or have blood or mucus	Severe abdominal pain

- The primary component of the immune-mediated colitis consisted of diarrhea
- Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis
- In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies

ASSESS

Assess the severity of the adverse reaction[2]

Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; peritoneal signs	Life-threatening consequences; urgent intervention indicated

MODIFY

Modify treatment based on severity

Withhold†	Permanently discontinue
For Grade 2 or 3	For Grade 4

- In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

†Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating corticosteroids.

SELECTED SAFETY INFORMATION

BAVENCIO can cause **immune-mediated type I diabetes mellitus**, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated type I diabetes mellitus occurred in 0.1% (2/1738) of patients, including Grade 3 (0.1%) adverse reactions.

BAVENCIO can cause **immune-mediated nephritis with renal dysfunction**. Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade 4 increased blood creatinine. Immune-mediated nephritis with renal dysfunction occurred in 0.1% (1/1738) of patients, which was a Grade 2 (0.1%) adverse reaction. Systemic corticosteroids were required in this patient.

Hepatotoxicity and immune-mediated hepatitis

Clinical trial experience

- BAVENCIO® (avelumab) can cause immune-mediated hepatitis
- Across clinical studies,* immune-mediated hepatitis occurred in 0.9% (16/1738) of patients receiving BAVENCIO, including:
  - Fatal (0.1%) adverse reactions
  - Grade 3 (0.6%) adverse reactions
  - Grade 2 (0.1%) adverse reactions
- Hepatitis led to permanent discontinuation of BAVENCIO in 0.5% and withholding of BAVENCIO in 0.2% of patients
- Systemic corticosteroids were required in all (16/16) patients with hepatitis
- Hepatitis resolved in 56% (9/16) of the patients
- Of the 3 patients in whom BAVENCIO was withheld for hepatitis, 3 reinitiated treatment with BAVENCIO after symptom improvement
  - Of these, none had recurrence of hepatitis

MONITOR

Monitor patients for signs and symptoms of hepatitis, including

Jaundice	Severe nausea or vomiting	Pain on the right side of abdomen
Dark urine		Easy bruising or bleeding

- Evaluate liver enzymes at baseline and periodically during treatment

ASSESS

Assess the severity of the adverse reaction[2]

Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic, intervention not indicated	Moderate symptoms; medical intervention indicated	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences; severe decompensated liver function (eg, coagulopathy, encephalopathy, coma)

MODIFY

Modify treatment based on severity

	Withhold†	Permanently discontinue
Hepatitis with no tumor involvement of the liver	For AST or ALT increases >3 and up to 8 times ULN, or total bilirubin increases >1.5 and up to 3 times ULN	For AST or ALT >8 times ULN or total bilirubin >3 times ULN
Hepatitis with tumor involvement of the liver‡	If baseline AST or ALT is >1 and up to 3 times ULN and increases to >5 and up to 10 times ULN, or baseline AST or ALT is >3 and up to 5 times ULN and increases to >8 and up to 10 times ULN	For AST or ALT increases to >10 times ULN or total bilirubin increases to >3 times ULN

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

- In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

†Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating corticosteroids.

‡If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue BAVENCIO based on recommendations for hepatitis where there is no tumor involvement of the liver.

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Immune-mediated endocrinopathies: adrenal insufficiency

Clinical trial experience

- BAVENCIO can cause primary or secondary adrenal insufficiency
- Across clinical studies,* immune-mediated adrenal insufficiency occurred in 0.5% (8/1738) of patients receiving BAVENCIO, including:
  - Grade 3 (0.1%) adverse reactions
  - Grade 2 (0.3%) adverse reactions
- Adrenal insufficiency led to permanent discontinuation of BAVENCIO in 0.1% and withholding of BAVENCIO in 0.1% of patients
- Systemic corticosteroids were required in all (8/8) patients with adrenal insufficiency
- Adrenal insufficiency did not resolve in any patient (0/8)
- Of the 2 patients in whom BAVENCIO was withheld for adrenal insufficiency, none reinitiated treatment with BAVENCIO

MONITOR

Monitor patients during and after treatment for signs and symptoms of adrenal insufficiency, including

Fatigue	Weight loss or weight gain	Dizziness or fainting
Hair loss	Changes in mood or behavior	

ASSESS

Assess the severity of the adverse reaction[2]

Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated

MODIFY

Modify treatment based on severity

Grade 2 or higher	Grade 3-4
Initiate symptomatic treatment, including hormone replacement, as clinically indicated	Withhold BAVENCIO for adrenal insufficiency until clinically stable, or permanently discontinue depending on severity

- In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

SELECTED SAFETY INFORMATION

BAVENCIO can cause **immune-mediated dermatologic adverse reactions**, including rash or dermatitis. Exfoliative dermatitis including Stevens Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold BAVENCIO for suspected and permanently discontinue for confirmed SJS, TEN, or DRESS. Immune-mediated dermatologic adverse reactions occurred in 5% (90/1738) of patients, including Grade 3 (0.1%) and Grade 2 (2.0%) adverse reactions. Systemic corticosteroids were required in 29% (26/90) of patients with dermatologic adverse reactions.

Immune-mediated endocrinopathies: hypophysitis

Clinical trial experience

- BAVENCIO® (avelumab) can cause immune-mediated hypophysitis. Hypophysitis can cause hypopituitarism
- Across clinical studies,* immune-mediated pituitary disorders occurred in 0.1% (1/1738) of patients receiving BAVENCIO, including:
  - Grade 2 (0.1%) adverse reactions
- Hypopituitarism did not lead to withholding of BAVENCIO in this patient
- Systemic corticosteroids were not required in this patient

MONITOR

Hypophysitis can present with acute symptoms associated with mass effect, such as

Headache	Photophobia	Visual field defects

ASSESS

Assess the severity of the adverse reaction[2]

Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated

ADL, activities of daily living.

MODIFY

Modify treatment based on severity

Any grade	Grade 3-4
Initiate hormone replacement as clinically indicated	Withhold BAVENCIO until clinically stable, or permanently discontinue depending on severity

- In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

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Immune-mediated endocrinopathies: thyroid disorders

Clinical trial experience

- BAVENCIO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism
- Across clinical studies,* thyroiditis occurred in 0.2% (4/1738) of patients receiving BAVENCIO, including:
  - Grade 2 (0.1%) adverse reactions
  - Thyroiditis did not lead to permanent discontinuation or withholding of BAVENCIO in any patients
  - No patients with thyroiditis required systemic corticosteroids
  - Thyroiditis did not resolve in any patients (0/4)
- Across clinical studies,* hyperthyroidism occurred in 0.4% (7/1738) of patients receiving BAVENCIO, including:
  - Grade 2 (0.3%) adverse reactions
  - Hyperthyroidism did not lead to permanent discontinuation of BAVENCIO in any patients and led to withholding of BAVENCIO in 0.1% of patients
  - Systemic corticosteroids were required in 29% (2/7) of patients with hyperthyroidism
  - Hyperthyroidism resolved in 86% (6/7) of the patients
  - Of the 2 patients in whom BAVENCIO was withheld for hyperthyroidism, 2 reinitiated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of hyperthyroidism
- Across clinical studies,* hypothyroidism occurred in 5% (90/1738) of patients receiving BAVENCIO, including:
  - Grade 3 (0.2%) adverse reactions
  - Grade 2 (3.7%) adverse reactions
  - Hypothyroidism led to permanent discontinuation of BAVENCIO in 0.1% and withholding of BAVENCIO in 0.5% of patients
  - Systemic corticosteroids were required in 7% (6/90) of patients with hypothyroidism
  - Hypothyroidism resolved in 4% (4/90) of the patients
  - Of the 8 patients in whom BAVENCIO was withheld for hypothyroidism, none reinitiated BAVENCIO

MONITOR

Monitor patients for signs and symptoms of thyroid disorders, including

Tachycardia	Increased sweating	Fatigue
Weight gain or weight loss	Unusual thirst or hunger	Hair loss
Feeling cold	Constipation	Changes in mood or behavior

ASSESS

Assess the severity of the adverse reaction[2]

Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression or replacement therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated

ADL, activities of daily living.

MODIFY

Modify treatment based on severity

Any grade hypothyroidism or hyperthyroidism	Grade 3-4
Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism, as clinically indicated	Withhold BAVENCIO until clinically stable, or permanently discontinue depending on severity

- In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

Immune-mediated endocrinopathies: type 1 diabetes mellitus, which can present with diabetic ketoacidosis

Clinical trial experience

- Type 1 diabetes mellitus, which can present with diabetic ketoacidosis
- Across clinical studies,* immune-mediated type 1 diabetes mellitus occurred in 0.1% (2/1738) of patients receiving BAVENCIO® (avelumab), including:
  - Grade 3 (0.1%) adverse reactions
- Type 1 diabetes mellitus led to permanent discontinuation of BAVENCIO in these two patients
- Type 1 diabetes mellitus did not lead to withholding of BAVENCIO in any patient
- Systemic corticosteroids were not required in any patient with Type 1 diabetes mellitus
- Type 1 diabetes mellitus resolved in no patient and all patients required ongoing insulin treatment

MONITOR

Monitor patients for hyperglycemia or other signs and symptoms of diabetes

ASSESS

Assess the severity of the adverse reaction[2]

Grade 1	Grade 2	Grade 3	Grade 4
Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated

MODIFY

Modify treatment based on severity

Hyperglycemia
Initiate treatment with insulin as clinically indicated. Withhold BAVENCIO until clinically stable or permanently discontinue depending on severity

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

SELECTED SAFETY INFORMATION

BAVENCIO can result in **other immune-mediated adverse reactions**. Other clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in patients who received BAVENCIO or were reported with the use of other PD-1/PD-L1 blocking antibodies. For **myocarditis**, permanently discontinue BAVENCIO for Grade 2, Grade 3, or Grade 4. For **neurological toxicities**, withhold BAVENCIO for Grade 2 and permanently discontinue for Grade 3 or Grade 4.

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BAVENCIO® avelumab Injection 20 mg/mL

Immune-mediated nephritis with renal dysfunction

Clinical trial experience

- BAVENCIO can cause immune-mediated nephritis
- Across clinical studies,* immune-mediated nephritis with renal dysfunction occurred in 0.1% (1/1738) of patients receiving BAVENCIO, including:
  - Grade 2 (0.1%) adverse reactions
- Nephritis with renal dysfunction led to permanent discontinuation of BAVENCIO in this patient
- Nephritis did not lead to withholding of BAVENCIO in any patient
- Systemic corticosteroids were required in this patient
- Nephritis with renal dysfunction did not resolve in this patient

MONITOR

Evaluate creatinine at baseline and periodically during treatment

ASSESS

Assess the severity of the adverse reaction[2]

Grade 1 creatinine increased	Grade 2 creatinine increased	Grade 3 creatinine increased	Grade 4 creatinine increased
>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN

ULN, upper limit of normal.

MODIFY

Modify treatment based on severity

Withhold†	Permanently discontinue
For Grade 2 or 3 increased blood creatinine	For Grade 4 increased blood creatinine

- In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

†Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating corticosteroids.

SELECTED SAFETY INFORMATION

BAVENCIO can cause severe or life-threatening **infusion-related reactions**. Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent infusions based upon clinical judgment and presence/severity of prior infusion reactions. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for Grade 1 or Grade 2 infusion-related reactions. Permanently discontinue BAVENCIO for Grade 3 or Grade 4 infusion-related reactions. Infusion-related reactions occurred in 25% of patients, including three (0.2%) Grade 4 and nine (0.5%) Grade 3 infusion-related reactions. Eleven (92%) of the 12 patients with Grade ≥3 reactions were treated with intravenous corticosteroids.

Fatal and other serious **complications of allogeneic hematopoietic stem cell transplantation (HSCT)** can occur in patients who receive HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

Immune-mediated dermatologic adverse reactions

Clinical trial experience

- BAVENCIO® (avelumab) can cause immune-mediated rash or dermatitis
- Exfoliative dermatitis, including Stevens Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies
- Across clinical studies,* immune-mediated dermatologic adverse reactions occurred in 5% (90/1738) of patients receiving BAVENCIO, including:
  - Grade 3 (0.1%) adverse reactions
  - Grade 2 (2.0%) adverse reactions
- Dermatologic adverse reactions led to permanent discontinuation of BAVENCIO in 0.3% of patients and withholding of BAVENCIO in 0.4% of patients
- Systemic corticosteroids were required in 29% (26/90) of patients with dermatologic adverse reactions
  - One patient required the addition of tacrolimus to high-dose corticosteroids
- Dermatologic adverse reactions resolved in 41% (37/90) of the patients
- Of the 7 patients in whom BAVENCIO was withheld for dermatologic adverse reactions, 3 reinitiated treatment with BAVENCIO after symptom improvement
  - Of these, none had recurrence of dermatologic adverse reaction

MONITOR

Monitor patients for signs and symptoms of rash or dermatitis

Rash	Itching	Skin blistering or peeling
Painful sores or ulcers in mouth or nose, throat, or genital area	Fever or flu-like symptoms	Swollen lymph nodes

ASSESS

Assess the severity of the adverse reaction[2]

Grade 1	Grade 2	Grade 3	Grade 4
–	–	SJS - skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment)	SJS - skin sloughing covering 10% to 30% BSA with associated signs TEN - skin sloughing covering ≥30% BSA with associated symptoms

BSA, body surface area.

MODIFY

Modify treatment based on severity

Withhold†	Permanently discontinue
For suspected SJS, TEN, or DRESS	For confirmed SJS, TEN, or DRESS

- Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes
- In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

†Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating corticosteroids.

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BAVENCIO® avelumab Injection 20 mg/mL

Other immune-mediated adverse reactions

Clinical trial experience

- The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received BAVENCIO or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions

Other immune-mediated adverse reactions	
Cardiac/Vascular	Myocarditis, pericarditis, vasculitis
Gastrointestinal	Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis
Nervous System	Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy
Ocular	Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada like syndrome, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss
Musculoskeletal and Connective Tissue	Myositis/polymyositis, rhabdomyolysis (and associated sequelae including renal failure), arthritis, polymyalgia rheumatic
Endocrine	Hypoparathyroidism
Other (Hematologic/Immune)	Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

- For myocarditis, permanently discontinue BAVENCIO for Grade 2, Grade 3, or Grade 4 adverse reactions
- For neurological toxicities, withhold BAVENCIO for Grade 2* and permanently discontinue for Grade 3 or Grade 4 adverse reactions

*Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating corticosteroids.

SELECTED SAFETY INFORMATION

BAVENCIO can cause **fetal harm** when administered to a pregnant woman. Advise patients of the potential risk to a fetus including the risk of fetal death. Advise females of childbearing potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO. It is not known whether BAVENCIO is excreted in human milk. Advise a lactating woman **not to breastfeed** during treatment and for at least 1 month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breastfed infants.

The most common adverse reactions (all grades, ≥20%) in patients with **metastatic Merkel cell carcinoma (MCC)** were fatigue (50%), musculoskeletal pain (32%), diarrhea (23%), nausea (22%), infusion-related reaction (22%), rash (22%), decreased appetite (20%), and peripheral edema (20%).

Selected treatment-emergent laboratory abnormalities (all grades, ≥20%) in patients with **metastatic MCC** were lymphopenia (49%), anemia (35%), increased aspartate aminotransferase (34%), thrombocytopenia (27%), and increased alanine aminotransferase (20%).

Infusion-related reactions

Clinical trial experience

- BAVENCIO can cause severe or life-threatening infusion-related reactions
- Across clinical studies,* infusion-related reactions occurred in 25% (439/1738; all grades) of patients, including:
  - 3 (0.2%) Grade 4 infusion-related reactions
  - 9 (0.5%) Grade 3 infusion-related reactions
- 93% (1615/1738) of patients received premedication with antihistamine and acetaminophen
- 11 (92%) of the 12 patients with Grade ≥3 reactions were treated with intravenous corticosteroids
- 14% of patients (252/1738) had infusion-related reactions that occurred after BAVENCIO infusion was completed
- 25.3% (439/1738) of patients experienced infusion-related reactions[1]
- The onset of infusion-related reactions was mostly at the initial infusions[1]:
  - 20.1% of patients experienced their first infusion-related reaction during the first infusion (n=1738 patients at risk)
  - 4.7% of patients experienced their first infusion-related reaction during their second infusion (n=1306 patients at risk)
  - 1.5% of patients experienced their first infusion-related reaction during their third infusion (n=1144 patients at risk)
  - 0.6% of patients experienced their first infusion-related reaction during their fourth infusion (n=937 patients at risk)
  - 0.7% of patients experienced their first infusion-related reaction during their fifth infusion or a subsequent infusion (n=841 patients at risk)

MONITOR

Monitor patients for signs and symptoms of infusion-related reactions, including

Pyrexia	Chills	Flushing
Hypotension	Dyspnea	Wheezing
Back pain	Abdominal pain	Urticaria

- Premedicate with an antihistamine and with acetaminophen prior to the first 4 infusions of BAVENCIO and subsequently as needed

ASSESS

Assess the severity of the adverse reactions[2]

Grade 1	Grade 2	Grade 3	Grade 4
Mild transient reaction; infusion interruption is not indicated; intervention is not indicated	Therapy or infusion interruption is indicated but the reaction responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications are indicated for less than 24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated

IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs.

MODIFY

Modify treatment based on severity

Grade 1-2	Grade 3-4
Interrupt or slow the rate of infusion	Stop the infusion and permanently discontinue BAVENCIO

*These data are from the JAVELIN Merkel 200 Trial and the JAVELIN Solid Tumor Trial.

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Complications of allogeneic hematopoietic stem cell transplantation

Clinical trial experience

- Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody
- Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause)
- These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT

MONITOR

Follow patients closely for evidence of transplant-related complications and intervene promptly

ASSESS

Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT

IMPORTANT SAFETY INFORMATION

BAVENCIO® (avelumab) can cause **severe and fatal immune-mediated adverse reactions** in any organ system or tissue and at any time after starting treatment with a PD-1/PD-L1 blocking antibody, including after discontinuation of treatment.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

No dose reduction for BAVENCIO is recommended. For immune-mediated adverse reactions, withhold or permanently discontinue BAVENCIO depending on severity. In general, withhold BAVENCIO for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue BAVENCIO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids. In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic corticosteroids (eg, endocrinopathies and dermatologic reactions) are discussed in subsequent sections.

BAVENCIO can cause **immune-mediated pneumonitis**. Withhold BAVENCIO for Grade 2, and permanently discontinue for Grade 3 or Grade 4 pneumonitis. Immune-mediated pneumonitis occurred in 1.2% (21/1738) of patients, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%), and Grade 2 (0.6%) adverse reactions. Systemic corticosteroids were required in all (21/21) patients with pneumonitis.

BAVENCIO can cause **immune-mediated colitis**. The primary component of immune-mediated colitis consisted of diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade 4 colitis. Immune-mediated colitis occurred in 1.5% (26/1738) of patients, including Grade 3 (0.4%) and Grade 2 (0.7%) adverse reactions. Systemic corticosteroids were required in all (26/26) patients with colitis.

BAVENCIO can cause **hepatotoxicity and immune-mediated hepatitis**. Withhold or permanently discontinue BAVENCIO based on tumor involvement of the liver and severity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin elevation. Immune-mediated hepatitis occurred with BAVENCIO as a single agent in 0.9% (16/1738) of patients, including fatal (0.1%), Grade 3 (0.6%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in all (16/16) patients with hepatitis.

BAVENCIO can cause primary or secondary **immune-mediated adrenal insufficiency**. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated adrenal insufficiency occurred in 0.5% (8/1738) of patients, including Grade 3 (0.1%) and Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in all (8/8) patients with adrenal insufficiency.

BAVENCIO can cause **immune-mediated hypophysitis**. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated pituitary disorders occurred in 0.1% (1/1738) of patients, which was a Grade 2 (0.1%) adverse reaction.

BAVENCIO can cause **immune-mediated thyroid disorders**. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Thyroiditis occurred in 0.2% (4/1738) of patients, including Grade 2 (0.1%) adverse reactions. Hyperthyroidism occurred in 0.4% (7/1738) of patients, including Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in 29% (2/7) of patients with hyperthyroidism. Hypothyroidism occurred in 5% (90/1738) of patients, including Grade 3 (0.2%) and Grade 2 (3.7%) adverse reactions. Systemic corticosteroids were required in 7% (6/90) of patients with hypothyroidism.

BAVENCIO can cause **immune-mediated type I diabetes mellitus**, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated type I diabetes mellitus occurred in 0.1% (2/1738) of patients, including Grade 3 (0.1%) adverse reactions.

BAVENCIO can cause **immune-mediated nephritis with renal dysfunction**. Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade 4 increased blood creatinine. Immune-mediated nephritis with renal dysfunction occurred in 0.1% (1/1738) of patients, which was a Grade 2 (0.1%) adverse reaction. Systemic corticosteroids were required in this patient.

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IMPORTANT SAFETY INFORMATION (cont'd)

BAVENCIO can cause **immune-mediated dermatologic adverse reactions**, including rash or dermatitis. Exfoliative dermatitis including Stevens Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold BAVENCIO for suspected and permanently discontinue for confirmed SJS, TEN, or DRESS. Immune-mediated dermatologic adverse reactions occurred in 5% (90/1738) of patients, including Grade 3 (0.1%) and Grade 2 (2.0%) adverse reactions. Systemic corticosteroids were required in 29% (26/90) of patients with dermatologic adverse reactions.

BAVENCIO can result in **other immune-mediated adverse reactions**. Other clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in patients who received BAVENCIO or were reported with the use of other PD-1/PD-L1 blocking antibodies. For **myocarditis**, permanently discontinue BAVENCIO for Grade 2, Grade 3, or Grade 4. For **neurological toxicities**, withhold BAVENCIO for Grade 2 and permanently discontinue for Grade 3 or Grade 4.

BAVENCIO can cause severe or life-threatening **infusion-related reactions**. Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent infusions based upon clinical judgment and presence/severity of prior infusion reactions. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for Grade 1 or Grade 2 infusion-related reactions. Permanently discontinue BAVENCIO for Grade 3 or Grade 4 infusion-related reactions. Infusion-related reactions occurred in 25% of patients, including three (0.2%) Grade 4 and nine (0.5%) Grade 3 infusion-related reactions. Eleven (92%) of the 12 patients with Grade ≥3 reactions were treated with intravenous corticosteroids.

Fatal and other serious **complications of allogeneic hematopoietic stem cell transplantation (HSCT)** can occur in patients who receive HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

BAVENCIO can cause **fetal harm** when administered to a pregnant woman. Advise patients of the potential risk to a fetus including the risk of fetal death. Advise females of childbearing potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO. It is not known whether BAVENCIO is excreted in human milk. Advise a lactating woman **not to breastfeed** during treatment and for at least 1 month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breastfed infants.

The most common adverse reactions (all grades, ≥20%) in patients with **metastatic Merkel cell carcinoma (MCC)** were fatigue (50%), musculoskeletal pain (32%), diarrhea (23%), nausea (22%), infusion-related reaction (22%), rash (22%), decreased appetite (20%), and peripheral edema (20%).

Selected treatment-emergent laboratory abnormalities (all grades, ≥20%) in patients with **metastatic MCC** were lymphopenia (49%), anemia (35%), increased aspartate aminotransferase (34%), thrombocytopenia (27%), and increased alanine aminotransferase (20%).

A **fatal adverse reaction** (sepsis) occurred in one (0.3%) patient with **locally advanced or metastatic urothelial carcinoma (UC)** receiving BAVENCIO + best supportive care (BSC) as first-line maintenance treatment. In patients with previously treated locally advanced or metastatic UC, fourteen patients (6%) who were treated with BAVENCIO experienced either pneumonitis, respiratory failure, sepsis/urosepsis, cerebrovascular accident, or gastrointestinal adverse events, which led to death.

The most common adverse reactions (all grades, ≥20%) in patients with **locally advanced or metastatic UC** receiving BAVENCIO + BSC (vs BSC alone) as first-line maintenance treatment were fatigue (35% vs 13%), musculoskeletal pain (24% vs 15%), urinary tract infection (20% vs 11%), and rash (20% vs 2.3%). In patients with previously treated locally advanced or metastatic UC receiving BAVENCIO, the most common adverse reactions (all grades, ≥20%) were fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection.

Selected laboratory abnormalities (all grades, ≥20%) in patients with **locally advanced or metastatic UC** receiving BAVENCIO + BSC (vs BSC alone) as first-line maintenance treatment were blood triglycerides increased (34% vs 28%), alkaline phosphatase increased (30% vs 20%), blood sodium decreased (28% vs 20%), lipase increased (25% vs 16%), aspartate aminotransferase (AST) increased (24% vs 12%), blood potassium increased (24% vs 16%), alanine aminotransferase (ALT) increased (24% vs 12%), blood cholesterol increased (22% vs 16%), serum amylase increased (21% vs 12%), hemoglobin decreased (28% vs 18%), and white blood cell decreased (20% vs 10%).

CoverOne® provides patient access and reimbursement support services to help eligible patients gain appropriate access to BAVENCIO® (avelumab)*

We recognize that each patient's situation is different, and are dedicated to helping eligible BAVENCIO patients one at a time.

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