BAVENCIO®
avelumab Injection 20 mg/mL

Dosing and Treatment Management Guide

THE FIRST AND ONLY **FDA-approved anti-PD-L1 immunotherapy for adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (mMCC)**[1]

APPROVED **for the treatment of patients with locally advanced or metastatic urothelial carcinoma (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**

These indications are approved under accelerated approval based on tumor response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

SELECTED SAFETY INFORMATION

BAVENCIO can cause **immune-mediated pneumonitis**, including fatal cases. Monitor patients for signs and symptoms of pneumonitis and evaluate suspected cases with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold BAVENCIO for moderate (Grade 2) and permanently discontinue for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis. Pneumonitis occurred in 1.2% (21/1738) of patients, including one (0.1%) patient with Grade 5, one (0.1%) with Grade 4, and five (0.3%) with Grade 3.

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BAVENCIO® (avelumab) dosing

Recommended dosage

10 mg/kg 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

BAVENCIO can cause **immune-mediated pneumonitis**, including fatal cases. Monitor patients for signs and symptoms of pneumonitis and evaluate suspected cases with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold BAVENCIO for moderate (Grade 2) and permanently discontinue for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis. Pneumonitis occurred in 1.2% (21/1738) of patients, including one (0.1%) patient with Grade 5, one (0.1%) with Grade 4, and five (0.3%) with Grade 3.

BAVENCIO can cause **immune-mediated hepatitis**, including fatal cases. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater hepatitis. Withhold BAVENCIO for moderate (Grade 2) immune-mediated hepatitis until resolution and permanently discontinue for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis. Immune-mediated hepatitis was reported in 0.9% (16/1738) of patients, including two (0.1%) patients with Grade 5, and 11 (0.6%) with Grade 3.

BAVENCIO can cause **immune-mediated colitis**. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold BAVENCIO until resolution for moderate or severe (Grade 2 or 3) colitis and permanently discontinue for life-threatening (Grade 4) or recurrent (Grade 3) colitis upon re-initiation of BAVENCIO. Immune-mediated colitis occurred in 1.5% (26/1738) of patients, including seven (0.4%) with Grade 3.

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 endocrinopathies**, including adrenal insufficiency, thyroid disorders, and type 1 diabetes mellitus.

Monitor patients for signs and symptoms of **adrenal insufficiency** during and after treatment, and administer corticosteroids as appropriate. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Adrenal insufficiency was reported in 0.5% (8/1738) of patients, including one (0.1%) with Grade 3.

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation. Manage hypothyroidism with hormone replacement therapy and hyperthyroidism with medical management. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) thyroid disorders. Thyroid disorders, including hypothyroidism, hyperthyroidism, and thyroiditis, were reported in 6% (98/1738) of patients, including three (0.2%) with Grade 3.

Type 1 diabetes mellitus including diabetic ketoacidosis: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Withhold BAVENCIO and administer anti-hyperglycemics or insulin in patients with severe or life-threatening (Grade ≥ 3) hyperglycemia, and resume treatment when metabolic control is achieved. Type 1 diabetes mellitus without an alternative etiology occurred in 0.1% (2/1738) of patients, including two cases of Grade 3 hyperglycemia.

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In metastatic MCC

Adverse reactions profile of 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 maculopapular, 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.

In locally advanced or metastatic UC

Adverse reactions profile of BAVENCIO

Adverse Reactions (≥ 10%)	BAVENCIO (N=242) All Grades %	Grade 3-4 %
Any	98	59
Gastrointestinal Disorders		
Nausea	24	1
Abdominal pain[a]	19	2
Diarrhea	18	2
Constipation	18	1
Vomiting/Retching	14	1
General Disorders and Administration Site Conditions		
Fatigue[b]	41	7
Infusion-related reaction[c]	30	0.4
Peripheral edema[d]	17	0.4
Pyrexia/Temperature increased	16	1
Infections		
Urinary tract infection[e]	21	5
Investigations		
Weight decreased	19	0
Metabolism and Nutrition Disorders		
Decreased appetite/Hypophagia	21	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[f]	25	3
Renal Disorders		
Creatinine increased/Renal failure[g]	16	3
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea/Exertional dyspnea	17	2
Cough/Productive cough	14	0
Skin and Subcutaneous Tissue Disorders		
Rash[h]	15	0.4
Pruritus/Generalized pruritus	10	0.4
Vascular Disorders		
Hypertension/Hypertensive crisis	10	5

[a] Includes abdominal discomfort, abdominal pain upper and lower, and gastrointestinal pain.
[b] Includes asthenia and malaise.
[c] Infusion-related reaction is a composite term that includes chills, pyrexia, back pain, flushing, dyspnea, and hypotension.
[d] Includes edema, generalized edema, and peripheral swelling.
[e] Includes urosepsis, cystitis, kidney infection, pyuria, and urinary tract infection due to fungus, bacterial, and enterococcus.
[f] Includes back pain, myalgia, neck pain, and pain in extremity.
[g] Includes acute kidney injury and glomerular filtration rate decreased.
[h] Includes dermatitis acneiform, eczema, erythema, erythema multiforme, erythematous, macular, maculopapular, papular, and pruritic rash.

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Summary of selected immune-mediated adverse reactions with BAVENCIO® (avelumab)

- The data described in this brochure are based on 2 trials, in which 1738 patients received BAVENCIO at doses of 10 mg/kg intravenously every 2 weeks
- This included 88 patients with metastatic MCC (JAVELIN Merkel 200 trial) and 242 patients with locally advanced and metastatic UC within the JAVELIN Solid Tumor trial
- In the JAVELIN Solid Tumor trial, 1650 patients were treated with BAVENCIO at doses of 10 mg/kg

Incidence and onset of selected immune-mediated adverse reactions

Adverse Reactions	Incidence (All Grades) n (%)	Time to Onset and Duration
Infusion-related reactions[2]	439 (25.3)	• 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)
Pneumonitis	21 (1.2)	• Median time to onset: 2.5 months (range: 3 days to 11 months) • Median duration: 7 weeks (range: 4 days to 4+ months)
Hepatitis	16 (0.9)	• Median time to onset: 3.2 months (range: 1 week to 15 months) • Median duration: 2.5 months (range: 1 day to 7.4+ months)
Colitis	26 (1.5)	• Median time to onset: 2.1 months (range: 2 days to 11 months) • Median duration of colitis: 6 weeks (range: 1 day to 14+ months)
Immune-mediated endocrinopathies: Adrenal insufficiency	8 (0.5)	• Median time to onset: 2.5 months (range: 1 day to 8 months)
Immune-mediated endocrinopathies: Thyroid disorders	98 (6.0)	• Median time to onset: 2.8 months (range: 2 weeks to 13 months) • Median duration: not estimable (range: 6 days to more than 26 months)

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:
  - 427 (25%) patients with Grade 1 or Grade 2 infusion-related reactions
  - 3 (0.2%) patients with Grade 4 infusion-related reactions
  - 9 (0.5%) patients with Grade 3 infusion-related reactions
    - 11 (92%) of the 12 patients with Grade ≥ 3 infusion-related reactions were treated with intravenous corticosteroids
  - 14% of patients (252/1738) had infusion-related reactions that occurred after BAVENCIO infusion was completed
- 93% (1615/1738) of patients received premedication with antihistamine and acetaminophen
- 25.3% (439/1738) of patients experienced infusion-related reactions
- The onset of infusion-related reactions was mostly at the initial infusions[2]:
  - 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)
  - 0.7% 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

ASSESS

Assess the severity of the adverse reaction[3]

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

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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Immune-mediated pneumonitis

Clinical trial experience

- BAVENCIO® (avelumab) can cause immune-mediated pneumonitis, including fatal cases
- Across clinical studies,* 1.2% (21/1738) of patients developed immune-mediated pneumonitis, including:
  - 1 (0.1%) patient with Grade 5 pneumonitis
  - 1 (0.1%) patient with Grade 4 pneumonitis
  - 5 (0.3%) patients with Grade 3 pneumonitis
- The median time to onset was 2.5 months (range: 3 days to 11 months) and the median duration of pneumonitis was 7 weeks (range: 4 days to 4+ months)
- Immune-mediated pneumonitis led to permanent discontinuation of BAVENCIO in 0.3% (6/1738) of patients
- All 21 patients were treated with corticosteroids
  - Pneumonitis resolved in 12 (57%) of the 21 patients at the time of data cut-off

MONITOR

Monitor patients for signs and symptoms of pneumonitis, including

New or worsening cough	Chest pain	Shortness of breath

- Evaluate patients with suspected pneumonitis with radiographic imaging

ASSESS

Assess the severity of the adverse reaction[3]

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

Corticosteroids	Grade 2	Grade 3-4 or Recurrent Grade 2
Grade ≥ 2: Administer corticosteroids (initial dose of 1-2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper)	Withhold BAVENCIO until resolution. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of pneumonitis after corticosteroid taper	Permanently discontinue BAVENCIO for Grade 2 recurrent, Grade 3, or Grade 4 pneumonitis

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

Immune-mediated hepatitis

Clinical trial experience

- BAVENCIO can cause immune-mediated hepatitis, including fatal cases
- Across clinical studies,* 0.9% (16/1738) of patients developed immune-mediated hepatitis, including:
  - 2 (0.1%) patients with Grade 5 immune-mediated hepatitis
  - 11 (0.6%) patients with Grade 3 immune-mediated hepatitis
- The median time to onset was 3.2 months (range: 1 week to 15 months), and the median duration of hepatitis was 2.5 months (range: 1 day to 7.4+ months)
- All 16 patients were treated with corticosteroids
  - Immune-mediated hepatitis resolved in 9 (56%) of the 16 patients at the time of data cut-off
- Immune-mediated hepatitis led to permanent discontinuation of BAVENCIO in 0.5% (9/1738) of patients

MONITOR

Monitor patients for signs and symptoms of hepatitis, including

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

- Monitor patients for abnormal liver tests prior to and periodically during treatment

ASSESS

Assess the severity of the adverse reaction[3]

Grade 1	Grade 3	Grade 4
Asymptomatic, treatment not indicated	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; reactivation of chronic hepatitis	Decompensated liver function (eg, ascites, coagulopathy, encephalopathy, coma)

MODIFY

Modify treatment based on severity

Corticosteroids	Grade 2	Grade 3-4
Grade ≥ 2: Administer corticosteroids (initial dose 1-2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper)	For AST, or ALT > 3 and up to 5 times ULN, or total bilirubin > 1.5 and up to 3 times ULN: Withhold BAVENCIO until resolution. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of hepatitis after corticosteroid taper	For AST or ALT > 5 times ULN or total bilirubin > 3 times ULN: Permanently discontinue BAVENCIO

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

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Immune-mediated colitis

Clinical trial experience

- BAVENCIO® (avelumab) can cause immune-mediated colitis
- Across clinical studies,* 1.5% (26/1738) of patients developed immune-mediated colitis including:
  - 7 (0.4%) patients with Grade 3 colitis
- The median time to onset was 2.1 months (range: 2 days to 11 months) and the median duration of colitis was 6 weeks (range: 1 day to 14+ months)
- All 26 patients were treated with corticosteroids
  - Immune-mediated colitis resolved in 18 (70%) of the 26 patients at the time of data cut-off
- Immune-mediated colitis led to permanent discontinuation of BAVENCIO in 0.5% (9/1738) of patients

MONITOR

Monitor patients for signs and symptoms of colitis, including		
Diarrhea	Blood in stool	Severe abdominal pain

ASSESS

Assess the severity of the adverse reaction[3]			
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; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated

MODIFY

Modify treatment based on severity		
Corticosteroids	**Grade 2-3**	**Grade 4 or Recurrent Grade 3**
Grade ≥ 2: Administer corticosteroids (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper)	Withhold BAVENCIO until resolution. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of colitis or diarrhea after corticosteroid taper	Permanently discontinue BAVENCIO

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

SELECTED SAFETY INFORMATION

BAVENCIO can cause **immune-mediated nephritis and renal dysfunction**. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater nephritis. Withhold BAVENCIO for moderate (Grade 2) or severe (Grade 3) nephritis until resolution to Grade 1 or lower. Permanently discontinue BAVENCIO for life-threatening (Grade 4) nephritis. Immune-mediated nephritis occurred in 0.1% (1/1738) of patients.

Immune-mediated endocrinopathies: adrenal insufficiency

Clinical trial experience

- BAVENCIO can cause immune-mediated endocrinopathies
- Across clinical studies,* 0.5% (8/1738) of patients developed adrenal insufficiency, including:
  - 1 (0.1%) patient with Grade 3 adrenal insufficiency
- The median time to onset was 2.5 months (range: 1 day to 8 months)
- Life-threatening consequences; urgent intervention indicated
- All 8 patients were treated with corticosteroids; 4 (50%) patients received high-dose corticosteroids
- Immune-mediated adrenal insufficiency led to permanent discontinuation of BAVENCIO in 0.1% (2/1738) of patients

MONITOR

Monitor patients during and after treatment for signs and symptoms of adrenal insufficiency, including		
Increased sweating	Changes in mood or behavior, such as irritability or forgetfulness	
Fatigue	Weight loss	Hypotension
Dizziness or fainting	Nausea or vomiting	Abdominal pain

ASSESS

Assess the severity of the adverse reaction[3]			
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	
Corticosteroids	**Grade 3-4**
Administer corticosteroids as appropriate for adrenal insufficiency	Withhold BAVENCIO for adrenal insufficiency until Grade 1 or resolved Resume BAVENCIO in patients with complete or partial resolution (Grade 0 or 1) of endocrinopathies after corticosteroid taper

*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® (avelumab) can cause immune-mediated thyroid disorders
- Across clinical studies,* 6% (98/1738) of patients developed immune-mediated thyroid disorders, including:
  - 3 (0.2%) patients with Grade 3 immune-mediated thyroid disorders
- Hypothyroidism occurred in 90 (5%) patients
- Hyperthyroidism occurred in 7 (0.4%) patients
- Thyroiditis occurred in 4 (0.2%) patients
- The median time to onset of immune-mediated thyroid disorders was 2.8 months (range: 2 weeks to 13 months) and the median duration was not estimable (range: 6 days to more than 26 months)
- Immune-mediated thyroid disorders led to discontinuation of BAVENCIO in 0.1% (2/1738) of patients
- In patients with locally advanced or metastatic UC, 4.5% (11/242) developed immune-related thyroid disorders, all of which were Grade 1 or 2
  - 9 patients had hypothyroidism
  - 2 patients had hyperthyroidism

MONITOR

Monitor patients for signs and symptoms of thyroid disorders, including

Tachycardia	Increased sweating
Feeling more hungry or thirsty than usual	Hair loss
Changes in mood or behavior, such as irritability or forgetfulness	Feeling cold

- Monitor patients at the start of treatment, periodically during treatment, and as indicated, based on clinical evaluation

ASSESS

Assess the severity of the adverse reaction[3]

Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression 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	Any Grade Hyperthyroidism	Grade 3-4 Thyroid Disorder
Manage with hormone replacement therapy	Initiate medical management for control of hyperthyroidism	Withhold BAVENCIO until Grade 1 or resolution after corticosteroid taper Resume BAVENCIO in patients with complete or partial resolution (Grade 0 or 1) of endocrinopathies after corticosteroid taper

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

Immune-mediated endocrinopathies: type 1 diabetes mellitus

Clinical trial experience

- BAVENCIO can cause type 1 diabetes mellitus, including diabetic ketoacidosis
- Across clinical studies,* type 1 diabetes mellitus without an alternative etiology occurred in 0.1% (2/1738) of patients
  - In 2 patients, Grade 3 hyperglycemia led to permanent discontinuation of BAVENCIO

MONITOR

Monitor patients for hyperglycemia or other signs and symptoms of diabetes

ASSESS

Assess the severity of the adverse reaction[3]

Grade 1	Grade 2	Grade 3	Grade 4
Fasting glucose value > ULN - 160 mg/dL; fasting glucose value > ULN - 8.9 mmol/L	Fasting glucose value > 160 - 250 mg/dL; fasting glucose value > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dL; > 13.9 - 27.8 mmol/L; hospitalization indicated	> 500 mg/dL; > 27.8 mmol/L; life-threatening consequences

MODIFY

Modify treatment based on severity

Grade 3-4 Hyperglycemia
Withhold BAVENCIO and administer antihyperglycemics or insulin
Resume treatment with BAVENCIO when metabolic control is achieved on insulin replacement or antihyperglycemics

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

SELECTED SAFETY INFORMATION

BAVENCIO can result in **other severe and fatal immune-mediated adverse reactions** involving any organ system during treatment or after treatment discontinuation. For suspected immune-mediated adverse reactions, evaluate to confirm or rule out an immune-mediated adverse reaction and to exclude other causes. Depending on the severity of the adverse reaction, withhold or permanently discontinue BAVENCIO, administer high-dose corticosteroids, and initiate hormone replacement therapy, if appropriate. Resume BAVENCIO when the immune-mediated adverse reaction remains at Grade 1 or lower following a corticosteroid taper. Permanently discontinue BAVENCIO for any severe (Grade 3) immune-mediated adverse reaction that recurs and for any life-threatening (Grade 4) immune-mediated adverse reaction. The following clinically significant immune-mediated adverse reactions occurred in less than 1% of 1738 patients treated with BAVENCIO: myocarditis with fatal cases, myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome, and systemic inflammatory response.

BAVENCIO can cause severe (Grade 3) or life-threatening (Grade 4) **infusion-related reactions**. Patients should be premedicated with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent doses 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 mild (Grade 1) or moderate (Grade 2) infusion-related reactions. Permanently discontinue BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Infusion-related reactions occurred in 25% (439/1738) of patients, including three (0.2%) patients with Grade 4 and nine (0.5%) with Grade 3.

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Immune-mediated nephritis and renal dysfunction

Clinical trial experience

- BAVENCIO® (avelumab) can cause immune-mediated nephritis
- Across clinical studies,* immune-mediated nephritis occurred in 0.1% (1/1738) of patients receiving BAVENCIO; BAVENCIO was permanently discontinued in this patient

MONITOR

Monitor patients for elevated serum creatinine prior to, and periodically during, treatment

ASSESS

Assess the severity of the adverse reaction[3]

Grade 1	Grade 2	Grade 3	Grade 4
Creatinine level increase of > 0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine > 3 x baseline or > 4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated

MODIFY

Modify treatment based on severity

Corticosteroids	Grade 2-3	Grade 4
Grade ≥ 2: Administer corticosteroids (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper)	For serum creatinine > 1.5 and up to 6 times ULN: Withhold BAVENCIO until Grade 1 or Grade 0, then resume after corticosteroid taper	For serum creatinine more than 6 times ULN: Permanently discontinue BAVENCIO

ULN, upper limit of normal.

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

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%).

The most common adverse reactions (all grades, ≥ 20%) in patients with **locally advanced or metastatic urothelial carcinoma (UC)** were fatigue (41%), infusion-related reaction (30%), musculoskeletal pain (25%), nausea (24%), decreased appetite/hypophagia (21%), and urinary tract infection (21%).

Other immune-mediated adverse reactions

Clinical trial experience

- BAVENCIO can result in severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system
- Most immune-mediated reactions initially manifest during BAVENCIO treatment; however, immune-mediated adverse reactions can occur after discontinuation of BAVENCIO
- The following clinically significant, immune-mediated adverse reactions occurred at an incidence of < 1% of 1738 patients treated with BAVENCIO for each of the following adverse reactions: immune-mediated myocarditis including fatal cases, immune-mediated myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome, and systemic inflammatory response*
- The following clinically significant immune-mediated adverse reactions have been reported with other products in this class: bullous dermatitis, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), pancreatitis, rhabdomyolysis, myasthenia gravis, histiocytic necrotizing lymphadenitis, demyelination, vasculitis, hemolytic anemia, hypophysitis, iritis, and encephalitis

MONITOR

For suspected immune-mediated adverse reactions, evaluate to confirm or rule out an immune-mediated adverse reaction and to exclude other causes

MODIFY

Modify treatment based on severity

Any Grade	Other Moderate or Severe Immune-Mediated Reactions or Grade 3-4 Endocrinopathies	Grade 2-3 (Persistent), Grade 3 (Recurrent), Life-Threatening,† or Requiring High-Dose Corticosteroids‡
Based on the severity of the event, withhold or permanently discontinue BAVENCIO, administer high-dose corticosteroids, and, if appropriate, initiate hormone replacement therapy	Withhold BAVENCIO pending clinical evaluation. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 or 1) of other immune-mediated adverse reactions after corticosteroid taper	Permanently discontinue BAVENCIO

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

†Excluding endocrinopathies.

‡≥ 10 mg/day prednisone or equivalent for > 12 weeks.

SELECTED SAFETY INFORMATION

Selected laboratory abnormalities (Grades 3-4, ≥ 3%) in patients with **locally advanced or metastatic UC** were hyponatremia (16%), increased gamma-glutamyltransferase (12%), lymphopenia (11%), hyperglycemia (9%), increased alkaline phosphatase (7%), anemia (6%), increased lipase (6%), hyperkalemia (3%), and increased aspartate aminotransferase (3%).

Please see the Important Safety Information on page 17. Click for the full Prescribing Information or visit BAVENCIO.com.

BAVENCIO® Injection 20 mg/mL
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IMPORTANT SAFETY INFORMATION

BAVENCIO® avelumab Injection 20 mg/mL

BAVENCIO can cause **immune-mediated pneumonitis**, including fatal cases. Monitor patients for signs and symptoms of pneumonitis and evaluate suspected cases with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold BAVENCIO for moderate (Grade 2) and permanently discontinue for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis. Pneumonitis occurred in 1.2% (21/1738) of patients, including one (0.1%) patient with Grade 5, one (0.1%) with Grade 4, and five (0.3%) with Grade 3.

BAVENCIO can cause **immune-mediated hepatitis**, including fatal cases. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater hepatitis. Withhold BAVENCIO for moderate (Grade 2) immune-mediated hepatitis until resolution and permanently discontinue for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis. Immune-mediated hepatitis was reported in 0.9% (16/1738) of patients, including two (0.1%) patients with Grade 5, and 11 (0.6%) with Grade 3.

BAVENCIO can cause **immune-mediated colitis**. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold BAVENCIO until resolution for moderate or severe (Grade 2 or 3) colitis and permanently discontinue for life-threatening (Grade 4) or recurrent (Grade 3) colitis upon re-initiation of BAVENCIO. Immune-mediated colitis occurred in 1.5% (26/1738) of patients, including seven (0.4%) with Grade 3.

BAVENCIO can cause **immune-mediated endocrinopathies**, including adrenal insufficiency, thyroid disorders, and type 1 diabetes mellitus.

Monitor patients for signs and symptoms of adrenal insufficiency during and after treatment, and administer corticosteroids as appropriate. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Adrenal insufficiency was reported in 0.5% (8/1738) of patients, including one (0.1%) with Grade 3.

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation. Manage hypothyroidism with hormone replacement therapy and hyperthyroidism with medical management. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) thyroid disorders. Thyroid disorders, including hypothyroidism, hyperthyroidism, and thyroiditis, were reported in 6% (98/1738) of patients, including three (0.2%) with Grade 3.

Type 1 diabetes mellitus including diabetic ketoacidosis: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Withhold BAVENCIO and administer anti-hyperglycemics or insulin in patients with severe or life-threatening (Grade ≥ 3) hyperglycemia, and resume treatment when metabolic control is achieved. Type 1 diabetes mellitus without an alternative etiology occurred in 0.1% (2/1738) of patients, including two cases of Grade 3 hyperglycemia.

BAVENCIO can cause **immune-mediated nephritis and renal dysfunction**. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater nephritis. Withhold BAVENCIO for moderate (Grade 2) or severe (Grade 3) nephritis until resolution to Grade 1 or lower. Permanently discontinue BAVENCIO for life-threatening (Grade 4) nephritis. Immune-mediated nephritis occurred in 0.1% (1/1738) of patients.

BAVENCIO can result in **other severe and fatal immune-mediated adverse reactions** involving any organ system during treatment or after treatment discontinuation. For suspected immune-mediated adverse reactions, evaluate to confirm or rule out an immune-mediated adverse reaction and to exclude other causes. Depending on the severity of the adverse reaction, withhold or permanently discontinue BAVENCIO, administer high-dose corticosteroids, and initiate hormone replacement therapy, if appropriate. Resume BAVENCIO when the immune-mediated adverse reaction remains at Grade 1 or lower following a corticosteroid taper. Permanently discontinue BAVENCIO for any severe (Grade 3) immune-mediated adverse reaction that recurs and for any life-threatening (Grade 4) immune-mediated adverse reaction. The following clinically significant immune-mediated adverse reactions occurred in less than 1% of 1738 patients treated with BAVENCIO: myocarditis with fatal cases, myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome, and systemic inflammatory response.

BAVENCIO can cause severe (Grade 3) or life-threatening (Grade 4) **infusion-related reactions**. Patients should be premedicated with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent doses 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 mild (Grade 1) or moderate (Grade 2) infusion-related reactions. Permanently discontinue BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Infusion-related reactions occurred in 25% (439/1738) of patients, including three (0.2%) patients with Grade 4 and nine (0.5%) with Grade 3.

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%).

The most common adverse reactions (all grades, ≥ 20%) in patients with **locally advanced or metastatic urothelial carcinoma (UC)** were fatigue (41%), infusion-related reaction (30%), musculoskeletal pain (25%), nausea (24%), decreased appetite/hypophagia (21%), and urinary tract infection (21%).

Selected laboratory abnormalities (Grades 3-4, ≥ 3%) in patients with **locally advanced or metastatic UC** were hyponatremia (16%), increased gamma-glutamyltransferase (12%), lymphopenia (11%), hyperglycemia (9%), increased alkaline phosphatase (7%), anemia (6%), increased lipase (6%), hyperkalemia (3%), and increased aspartate aminotransferase (3%).

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References: 1. U.S. National Library of Medicine. DailyMed: Advanced Search. Indication And Usage Section (34067-9). https://dailymed.nlm.nih.gov/dailymed/advanced-search.cfm. Accessed October 31, 2017. **2.** Data on file. Rockland, Mass: EMD Serono, Inc; 2017. **3.** Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. National Institutes of Health. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed October 31, 2017.

November 2017 US/AVE/0917/0349a