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RESEARCH**

APPLICATION NUMBER:

761049Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

BAVENCIO® (avelumab) injection, for intravenous use

Initial U.S. Approval: 2017

INDICATIONS AND USAGE

BAVENCIO is a programmed death ligand-1 (PD-L1) blocking antibody indicated for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC). (1)

This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1, 14)

DOSAGE AND ADMINISTRATION

- Administer 10 mg/kg as an intravenous infusion over 60 minutes every 2 weeks. (2.1)
- Premedicate with acetaminophen and an antihistamine for the first 4 infusions and subsequently as needed. (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: 200 mg/10 mL (20 mg/mL) solution in single-dose vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Immune-mediated pneumonitis: Withhold for moderate pneumonitis; permanently discontinue for severe, life-threatening or recurrent moderate pneumonitis. (5.1)

- Immune-mediated hepatitis: Monitor for changes in liver function. Withhold for moderate hepatitis; permanently discontinue for severe or life-threatening hepatitis. (5.2)
- Immune-mediated colitis: Withhold for moderate or severe colitis; permanently discontinue for life-threatening or recurrent severe colitis. (5.3)
- Immune-mediated endocrinopathies: Withhold for severe or life-threatening endocrinopathies (5.4)
- Immune-mediated nephritis and renal dysfunction: Withhold for moderate or severe nephritis and renal dysfunction; permanently discontinue for life-threatening nephritis or renal dysfunction. (5.5)
- Infusion-related reactions: Interrupt or slow the rate of infusion for mild or moderate infusion-related reactions. Stop the infusion and permanently discontinue BAVENCIO for severe or life-threatening infusion-related reactions. (5.7)
- Embryo-fetal toxicity: BAVENCIO can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.8, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (reported in $\geq 20\%$ of patients) were fatigue, musculoskeletal pain, diarrhea, nausea, infusion-related reaction, rash, decreased appetite, and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact EMD Serono at 1-800-283-8088 ext. 5563 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for **PATIENT COUNSELING INFORMATION** and Medication Guide.

Revised: 3/2017

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BAVENCIO is indicated for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC).

This indication is approved under accelerated approval based on tumor response and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials [\[see Clinical Studies \(14\)\]](#).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of BAVENCIO is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

2.2 Premedication

Premedicate patients with an antihistamine and 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 [\[see Warnings and Precautions \(5.7\)\]](#).

2.3 Dose Modifications

Recommended dose modifications of BAVENCIO for adverse reactions are provided in Table 1. Detailed information regarding clinical and laboratory monitoring guidelines for early detection of adverse reactions of BAVENCIO and recommended management (immunosuppressant treatment guidelines) are described in Warnings and Precautions (5).

Table 1: Recommended Dose Modifications of BAVENCIO for Adverse Reactions

Treatment-Related Adverse Reaction	Severity of Adverse Reactions*	Dose Modification
Pneumonitis [see Warnings and Precautions (5.1)]	Grade 2 pneumonitis	Withhold BAVENCIO. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of pneumonitis after corticosteroid taper.
	Grade 3 or 4 pneumonitis or recurrent Grade 2 pneumonitis	Permanently discontinue

Treatment-Related Adverse Reaction	Severity of Adverse Reactions*	Dose Modification
Hepatitis [<i>see Warnings and Precautions (5.2)</i>]	Aspartate aminotransferase (AST)/or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	Withhold BAVENCIO. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of hepatitis after corticosteroid taper.
	AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal	Permanently discontinue.
Colitis [<i>see Warnings and Precautions (5.3)</i>]	Grade 2 or 3 diarrhea or colitis	Withhold BAVENCIO. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of colitis or diarrhea after corticosteroid taper.
	Grade 4 diarrhea or colitis or recurrent Grade 3 diarrhea or colitis	Permanently discontinue.
Endocrinopathies (including but not limited to hypothyroidism, hyperthyroidism, adrenal insufficiency, hyperglycemia) [<i>see Warnings and Precautions (5.4)</i>]	Grade 3 or 4	Withhold BAVENCIO. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of endocrinopathies after corticosteroid taper.
Nephritis and Renal Dysfunction [<i>see Warnings and Precautions (5.5)</i>]	Serum creatinine more than 1.5 and up to 6 times the upper limit of normal	Withhold BAVENCIO. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of nephritis and renal dysfunction after corticosteroid taper.
	Serum creatinine more than 6 times the upper limit of normal	Permanently discontinue.

Treatment-Related Adverse Reaction	Severity of Adverse Reactions*	Dose Modification
Other immune-mediated adverse reactions (including but not limited to myocarditis, myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome, 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)** [see Warnings and Precautions (5.6)]	For any of the following: - Moderate or severe clinical signs or symptoms of an immune-mediated adverse reaction not described above - Grade 3 or 4 endocrinopathies	Withhold BAVENCIO pending clinical evaluation. Resume BAVENCIO in patients with complete or partial resolution (Grade 0 to 1) of other immune-mediated adverse reactions after corticosteroid taper.
	For any of the following: - Life threatening adverse reaction (excluding endocrinopathies) - Recurrent severe immune-mediated adverse reaction - Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks - Persistent Grade 2 or 3 immune-mediate adverse reactions lasting 12 weeks or longer	Permanently discontinue.
Infusion-related reaction [see Warnings and Precautions (5.7)]	Grade 1 or 2	Interrupt or slow the rate of infusion.
	Grade 3 or 4	Permanently discontinue.

* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4)

** Observed with BAVENCIO or with other anti-PD-1/PD-L1 monoclonal antibodies

2.4 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 and 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.

Storage of diluted BAVENCIO 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 diluted solution.

Administration

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

3 DOSAGE FORMS AND STRENGTHS

Injection: 200 mg/10 mL (20 mg/mL), clear, colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

BAVENCIO can cause immune-mediated pneumonitis, including fatal cases [[see Adverse Reactions \(6.1\)](#)]. Monitor patients for signs and symptoms of pneumonitis and evaluate patients with suspected pneumonitis with radiographic imaging. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper) for Grade 2 or greater pneumonitis. Withhold BAVENCIO for moderate (Grade 2) pneumonitis, and permanently discontinue for severe (Grade 3), life-threatening (Grade 4) or recurrent moderate (Grade 2) pneumonitis [[see Dosage and Administration \(2.3\)](#)].

Pneumonitis occurred in 1.2% (21/1738) of patients receiving BAVENCIO including one (0.1%) patient with Grade 5, one (0.1%) with Grade 4, and five (0.3%) with Grade 3 pneumonitis. Immune-mediated pneumonitis led to permanent discontinuation of BAVENCIO in 0.3% (6/1738) of patients. Among the 21 patients with immune-mediated 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). All 21 patients were treated with

systemic corticosteroids; 17 (81%) of the 21 patients received high-dose corticosteroids for a median of 8 days (range: 1 day to 2.3 months). Resolution of pneumonitis occurred in 12 (57%) of the 21 patients at the time of data cut-off.

5.2 Immune-Mediated Hepatitis

BAVENCIO can cause immune-mediated hepatitis including fatal cases [[see Adverse Reactions \(6.1\)](#)]. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper) 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 [[see Dosage and Administration \(2.3\)](#)].

Immune-mediated hepatitis occurred in 0.9% (16/1738) of patients receiving BAVENCIO including two (0.1%) patients with Grade 5 and 11 (0.6 %) patients with Grade 3 immune-mediated hepatitis. Immune-mediated hepatitis led to permanent discontinuation of BAVENCIO in 0.5% (9/1738) of patients. Among the 16 patients with 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; 15 (94%) of the 16 patients received high-dose corticosteroids for a median of 14 days (range: 1 day to 2.5 months). Resolution of hepatitis occurred in nine (56%) of the 16 patients at the time of data cut-off.

5.3 Immune-Mediated Colitis

BAVENCIO can cause immune-mediated colitis [[see Adverse Reactions \(6.1\)](#)]. Monitor patients for signs and symptoms of colitis. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper) for Grade 2 or greater colitis. Withhold BAVENCIO for moderate or severe (Grade 2 or 3) colitis until resolution. Permanently discontinue BAVENCIO for life-threatening (Grade 4) or for recurrent (Grade 3) colitis upon re-initiation of BAVENCIO [[see Dosage and Administration \(2.3\)](#)].

Immune-mediated colitis occurred in 1.5% (26/1738) of patients receiving BAVENCIO including seven (0.4%) patients with Grade 3 colitis. Immune-mediated colitis led to permanent discontinuation of BAVENCIO in 0.5% (9/1738) of patients. Among the 26 patients with immune-mediated 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; 15 (58%) of the 26 patients received high-dose corticosteroids for a median of 19 days (range: 1 day to 2.3 months). Resolution of colitis occurred in 18 (70%) of the patients at the time of data cut-off.

5.4 Immune-Mediated Endocrinopathies

BAVENCIO can cause immune-mediated endocrinopathies [[see Adverse Reactions \(6.1\)](#)].

Adrenal Insufficiency

Monitor patients for signs and symptoms of adrenal insufficiency during and after treatment. Administer corticosteroids as appropriate for adrenal insufficiency. Withhold BAVENCIO for severe (Grade 3) or life threatening (Grade 4) adrenal insufficiency [[see Dosage and Administration \(2.3\)](#)].

Adrenal insufficiency occurred in 0.5% (8/1738) of patients receiving BAVENCIO including one patient (0.1%) with Grade 3 adrenal insufficiency. Immune-mediated adrenal insufficiency led to permanent discontinuation of BAVENCIO in 0.1% (2/1738) of patients. Among the 8 patients with immune-mediated adrenal insufficiency, the median time to onset was 2.5 months (range: 1 day to 8 months). All eight patients were treated with corticosteroids; four (50%) of the eight patients received high-dose corticosteroids for a median of 1 day (range: 1 day to 24 days).

Thyroid Disorders (Hypothyroidism/Hyperthyroidism)

BAVENCIO can cause immune-mediated thyroid disorders. 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. Initiate medical management for control of hyperthyroidism. Withhold BAVENCIO for severe (Grade 3) or life threatening (Grade 4) thyroid disorders [[see Dosage and Administration \(2.3\)](#)].

Immune-mediated thyroid disorders occurred in 6% (98/1738) of patients receiving BAVENCIO including 3 (0.2%) Grade 3 immune-mediated thyroid disorders. Immune-mediated thyroid disorders led to discontinuation of BAVENCIO in 0.1% (2/1738) of patients. Hypothyroidism occurred in 90 (5%) patients, hyperthyroidism in seven (0.4%), and thyroiditis in four (0.2%) patients treated with BAVENCIO. Among the 98 patients with immune-mediated thyroid disorders, the median time to onset 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 resolved in seven (7%) of the 98 patients.

Type 1 Diabetes Mellitus

BAVENCIO can cause 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. Resume treatment with BAVENCIO when metabolic control is achieved on insulin replacement or anti-hyperglycemics [[see Dosage and Administration \(2.3\)](#)].

Type 1 diabetes mellitus without an alternative etiology occurred in 0.1% (2/1738) of patients including two cases of Grade 3 hyperglycemia that led to permanent discontinuation of BAVENCIO.

5.5 Immune-Mediated Nephritis and Renal Dysfunction

BAVENCIO can cause immune-mediated nephritis [[see Adverse Reactions \(6.1\)](#)]. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper) for Grade 2 or greater nephritis. Withhold BAVENCIO for moderate (Grade 2) or severe (Grade 3) nephritis until resolution to $\leq$ Grade 1. Permanently discontinue BAVENCIO for life-threatening (Grade 4) nephritis [[see Dosage and Administration \(2.3\)](#)].

Immune-mediated nephritis occurred in 0.1% (1/1738) of patients receiving BAVENCIO; BAVENCIO was permanently discontinued in this patient.

5.6 Other Immune-Mediated Adverse Reactions

BAVENCIO can result in severe and fatal immune-mediated adverse reactions [[see Adverse Reactions \(6.1\)](#)]. 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.

For suspected immune-mediated adverse reactions, evaluate to confirm or rule out an immune-mediated adverse reaction and to exclude other causes. Depending upon the severity of the adverse reaction, withhold or permanently discontinue BAVENCIO, administer high dose corticosteroids, and if appropriate, initiate hormone replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper. Resume BAVENCIO when the immune-mediated adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue BAVENCIO for any severe (Grade 3) immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction [[see Dosage and Administration \(2.3\)](#)].

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 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.

5.7 Infusion-Related Reactions

BAVENCIO can cause severe or life-threatening infusion-related reactions [see [Adverse Reactions \(6.1\)](#)]. Premedicate with antihistamine and acetaminophen prior to the first 4 infusions. 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 or moderate infusion-related reactions. Stop the infusion and permanently discontinue BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions [see [Dosage and Administration \(2.3\)](#) and [Adverse Reactions \(6.1\)](#)].

Infusion-related reactions occurred in 25% (439/1738) of patients treated with BAVENCIO including three (0.2%) Grade 4 and nine (0.5%) Grade 3 infusion-related reactions. Ninety-three percent (1615/1738) of patients received premedication with antihistamine and acetaminophen. Eleven (92%) of the 12 patients with Grade ≥ 3 reactions were treated with intravenous corticosteroids.

5.8 Embryo-Fetal Toxicity

Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. If this drug is used during pregnancy, or if the patient becomes pregnant while taking BAVENCIO, inform the patient of the potential risk to a fetus. Advise females of childbearing potential to use effective contraception during treatment with BAVENCIO and for at least one month after the last dose of BAVENCIO [see [Use in Specific Populations \(8.1, 8.3\)](#)].

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the label:

- Immune-mediated pneumonitis [see [Warnings and Precautions \(5.1\)](#)]
- Immune-mediated hepatitis [see [Warnings and Precautions \(5.2\)](#)]
- Immune-mediated colitis [see [Warnings and Precautions \(5.3\)](#)]
- Immune-mediated endocrinopathies [see [Warnings and Precautions \(5.4\)](#)]
- Immune-mediated nephritis and renal dysfunction [see [Warnings and Precautions \(5.5\)](#)]
- Other immune-mediated adverse reactions [see [Warnings and Precautions \(5.6\)](#)]
- Infusion-related reactions [see [Warnings and Precautions \(5.7\)](#)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the Warnings and Precautions section include clinically significant adverse reactions occurring in 1738 patients exposed to BAVENCIO at 10 mg/kg intravenously (IV) every 2 weeks in a single-arm, multi-center, dose-finding and activity-estimating study (n=1650) with 16 disease-specific cohorts and in a single-arm, multi-center study (N=88) in patients with metastatic MCC.

The following criteria were used to classify an adverse reaction as immune-mediated: onset within 90 days after last dose of BAVENCIO, no spontaneous resolution within 7 days of onset, treatment with corticosteroids or other immunosuppressant or hormone replacement therapy, biopsy consistent with immune-mediated reaction, and no other clear etiology.

The study population characteristics of the 1738 patients were: median age of 64 years (range: 19 to 91 years); 52% male; 78% White, 9% Asian, 5% Black or African American and 8% other ethnic groups; ECOG performance score of 0 (38%), 1 (62%) or > 1 (0.4%); and the underlying malignancies were: non-small cell lung cancer (20%), gastric and gastroesophageal cancer (15%), urothelial cancer (14%), ovarian cancer (13%), metastatic breast cancer (10%), head and neck cancer (9%), metastatic MCC (5%), mesothelioma, renal cell carcinoma, melanoma, adrenocortical carcinoma (3% each), colorectal cancer, castrate-resistant prostate cancer, and unknown (1% each). In this population, 24% of patients were exposed to BAVENCIO for ≥ 6 months and 7% were exposed to BAVENCIO for ≥ 12 months.

The data described below reflect exposure to BAVENCIO 10 mg/kg intravenously every 2 weeks in 88 patients with metastatic MCC enrolled in the JAVELIN Merkel 200 trial. Patients with any of the following were excluded: autoimmune disease; medical conditions requiring systemic immunosuppression; prior organ or allogeneic stem cell transplantation; prior treatment with anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibodies; central nervous system (CNS) metastases; infection with HIV, hepatitis B or hepatitis C; or ECOG performance score ≥ 2 .

The median duration of exposure to BAVENCIO was 4 months (range: 2 weeks to 21 months). Forty percent of patients received BAVENCIO for more than 6 months and 14% were treated for more than one year [*see Clinical Studies (14)*]. The study population characteristics were: median age of 73 years (range: 33 to 88), 74% male, 92% White, ECOG performance score of 0 (56%) or 1 (44%), and 65% of patients had one prior anti-cancer therapy for metastatic MCC and 35% had two or more prior therapies.

BAVENCIO was permanently discontinued for adverse reactions in six (7%) patients; adverse reactions resulting in permanent discontinuation were ileus, Grade 3 transaminitis, Grade 3 creatine kinase elevation, tubulointerstitial nephritis, and Grade 3 pericardial effusion. BAVENCIO was temporarily discontinued in 21 (24%) patients for adverse events, excluding temporary dose interruption for infusion-related reactions where infusion was restarted the same day. The most common adverse reaction requiring dose interruption was anemia. Serious adverse reactions that occurred in more than one patient were acute kidney injury, anemia, abdominal pain, ileus, asthenia, and cellulitis. The most common adverse reactions ($\geq 20\%$) were fatigue, musculoskeletal pain, diarrhea, nausea, infusion-related reaction, rash, decreased appetite, and peripheral edema.

Table 2 and Table 3 summarize the incidence of adverse reactions and laboratory abnormalities, respectively, that occurred in patients receiving BAVENCIO.

Table 2: Adverse Reactions in $\geq 10\%$ of Patients Receiving BAVENCIO in the JAVELIN Merkel 200 Trial

Adverse Reactions	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	0
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

Table 3: Selected Treatment-Emergent* Laboratory Abnormalities in Patients Receiving BAVENCIO in the JAVELIN Merkel 200 Trial

Laboratory Tests	Any Grade (N=88) %	Grade 3-4 (N=88) %
Chemistry		
Increased aspartate aminotransferase (AST)	34	1
Increased alanine aminotransferase (ALT)	20	5
Increased lipase	14	4
Increased amylase	8	1
Increased bilirubin	6	1
Hyperglycemia**	-	7
Hematology		
Anemia	35	9
Lymphopenia	49	19
Thrombocytopenia	27	1
Neutropenia	6	1

* Treatment emergent consists of new onset of laboratory abnormality or worsening of baseline laboratory abnormality

** Hyperglycemia limited to Grade ≥ 3 events since fasting measurements were not obtained routinely

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to avelumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Of 1738 patients treated with BAVENCIO 10 mg/kg as an intravenous infusion every 2 weeks, 1558 were evaluable for treatment-emergent anti-drug antibodies (ADA) and 64 (4.1%) tested positive. The development of treatment-emergent ADA against avelumab did not appear to alter the pharmacokinetic profile or risk of infusion-related reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. There are no available data on the use of BAVENCIO in pregnant women [[see Clinical Pharmacology \(12.1\)](#)]. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death [[see Data](#)]. Human IgG1 immunoglobulins (IgG1) are known to cross the placenta. Therefore, BAVENCIO has the potential to be transmitted from the mother to the developing fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with BAVENCIO to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering BAVENCIO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to BAVENCIO may increase the risk of developing immune-related disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of avelumab in human milk, the effects on the breastfed infant, or the effects on milk production. Since many drugs including antibodies are excreted in human milk, advise a lactating woman not to breastfeed during treatment and for at least one month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breastfed infants.

8.3 Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman [[see Use in Specific Populations \(8.1\)](#)]. Advise females of reproductive potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO.

8.4 Pediatric Use

The safety and effectiveness of BAVENCIO have been established in pediatric patients age 12 years and older. Use of BAVENCIO in this age group is supported by evidence from adequate and well-controlled studies of BAVENCIO in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the steady state exposure of avelumab, that drug exposure is generally similar between adults and pediatric patients age 12 years and older for monoclonal antibodies, and that the course of MCC is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients. The recommended dose in pediatric patients 12 years of age or greater is the same as that in adults [*see Dosage and Administration (2.1), Clinical Pharmacology (12.3), and Clinical Studies (14)*].

Safety and effectiveness of BAVENCIO have not been established in pediatric patients less than 12 years of age.

8.5 Geriatric Use

Of the 88 patients with metastatic MCC treated with BAVENCIO, 75% were 65 years or over. However, clinical studies of BAVENCIO in metastatic MCC had fewer than 100 patients aged 65 and over, therefore, a determination cannot be made as to whether geriatric patients respond differently than younger patients.

10 OVERDOSAGE

No information on BAVENCIO overdose is available.

11 DESCRIPTION

Avelumab is a programmed death ligand-1 (PD-L1) blocking antibody. Avelumab is a human IgG1 lambda monoclonal antibody that has a molecular weight of approximately 147 kDa.

BAVENCIO (avelumab) Injection for intravenous use is a sterile, preservative-free, non-pyrogenic, clear, colorless to slightly yellow solution. Each single-dose vial contains 200 mg avelumab in 10 mL (20 mg/mL). Each mL contains 20 mg avelumab, D-mannitol (51 mg), glacial acetic acid (0.6 mg), polysorbate 20 (0.5 mg), sodium hydroxide (0.3 mg), and Water for Injection. The pH range of the solution is 5.0 – 5.6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PD-L1 may be expressed on tumor cells and tumor-infiltrating immune cells and can contribute to the inhibition of the anti-tumor immune response in the tumor microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This interaction releases the inhibitory effects of PD-L1 on the immune response resulting in the restoration of immune responses, including anti-tumor immune responses. Avelumab has also been shown to induce antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in decreased tumor growth.

12.3 Pharmacokinetics

The pharmacokinetics of avelumab was studied in 1629 patients who received doses ranging from 1 to 20 mg/kg every 2 weeks. The data showed that the exposure of avelumab increased dose-proportionally in the dose range of 10 to 20 mg/kg every 2 weeks. Steady-state concentrations of avelumab were reached after approximately 4 to 6 weeks (2 to 3 cycles) of repeated dosing, and the systemic accumulation was approximately 1.25-fold.

Distribution

The geometric mean volume of distribution at steady state for a subject receiving 10 mg/kg was 4.72 L.

Elimination

The primary elimination mechanism of avelumab is proteolytic degradation. Based on population pharmacokinetic analyses in patients with solid tumors, the total systemic clearance was 0.59 L/day and the terminal half-life was 6.1 days in patients receiving 10 mg/kg. In a post hoc analysis, avelumab clearance was found to decrease over time in patients with MCC, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline value of approximately 41.7% (40.0%).

Specific populations

Body weight was positively correlated with total systemic clearance in population pharmacokinetic analyses. No clinically meaningful differences in pharmacokinetics were observed in the clearance of avelumab based on age; sex; race; PD-L1 status; tumor burden; mild [calculated creatinine clearance (CLcr) 60 to 89 mL/min, n=623 as estimated by the Cockcroft-Gault formula], moderate [CLcr 30 to 59 mL/min, n=320] or severe [CLcr 15 to 29 mL/min, n=4] renal impairment; and mild [bilirubin less than or equal to ULN and AST greater than ULN or bilirubin between 1 and 1.5 times ULN, n=217] or moderate [bilirubin between 1.5 and 3 times ULN; n=4] hepatic impairment. There are limited data from patients with severe hepatic impairment [bilirubin greater than 3 times ULN, n=1], and the effect of severe hepatic impairment on the pharmacokinetics of avelumab is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to assess the potential of avelumab for genotoxicity or carcinogenicity.

Fertility studies have not been conducted with avelumab; however, an assessment of male and female reproductive organs was included in 3-month repeat-dose toxicity study in Cynomolgus monkeys. Weekly administration of avelumab did not result in any notable effects in the male and female reproductive organs.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. *M. tuberculosis*-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-L1 and PD-1 knockout mice and mice receiving PD-L1 blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

The efficacy and safety of BAVENCIO was demonstrated in the JAVELIN Merkel 200 trial (NCT02155647), an open-label, single-arm, multi-center study conducted in patients with histologically confirmed metastatic MCC whose disease had progressed on or after chemotherapy administered for distant metastatic disease. The trial excluded patients with autoimmune disease; medical conditions requiring systemic immunosuppression; prior organ or allogeneic stem cell transplantation; prior treatment with anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibodies; CNS metastases; infection with HIV, hepatitis B or hepatitis C; or ECOG performance score ≥ 2 .

Patients received BAVENCIO 10 mg/kg as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. Patients with radiological disease progression not associated with significant clinical deterioration, defined as no new or worsening symptoms, no change in performance status for greater than 2 weeks, and no need for salvage therapy, could continue treatment. Tumor response assessments were performed every 6 weeks. The major efficacy outcome measures were confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by a blinded independent central review committee (IRC) and IRC-assessed duration of response. The efficacy analysis was conducted when the last patient enrolled had completed 12 months of follow-up.

A total of 88 patients were enrolled. Baseline patient characteristics were a median age of 73 years (range: 33 to 88), 74% of patients were male, 92% were White, and the ECOG performance score was 0 (56%) or 1 (44%). Seventy-five percent of patients were 65 years or older, 35% were 75 or older and 3% were 85 or older. Sixty-five percent of patients were reported to have had one prior anti-cancer therapy for metastatic MCC and 35% had two or more prior therapies. Fifty-three percent of patients had visceral metastases. All patients had tumor samples evaluated for PD-L1 expression; of these, 66% were PD-L1-positive ($\geq 1\%$ of tumor cells), 18% were PD-L1 negative, and 16% had non-evaluable results by an investigational

immunohistochemistry assay. Archival tumor samples were evaluated for Merkel cell polyomavirus (MCV) using an investigational assay; of the 77 patients with evaluable results, 52% had evidence of MCV.

Efficacy results are presented in Table 4. Responses were observed in patients regardless of tumor PD-L1 expression or presence of MCV.

Table 4: Efficacy Results of the JAVELIN Merkel 200 Trial

Efficacy Endpoints	Results (N=88)
Overall Response Rate (ORR)	
Overall response rate, (95% CI)	33.0% (23.3%, 43.8%)
Complete response (CR) rate, (95% CI)	11.4% (6.6%, 19.9%)
Partial response (PR) rate, (95% CI)	21.6% (13.5%, 31.7%)
Duration of Response (DOR)	N=29
Range in months	2.8 to 23.3+
Patients with DOR $\geq$ 6 months, n (%)	25 (86%)
Patients with DOR $\geq$ 12 months, n (%)	13 (45%)

CI: Confidence interval

16 HOW SUPPLIED/STORAGE AND HANDLING

BAVENCIO (avelumab) Injection is a sterile, preservative-free, and clear, colorless to slightly yellow solution for intravenous infusion supplied as a single-dose vial of 200 mg/10 mL (20 mg/mL), individually packed into a carton (NDC 44087-3535-1).

Store refrigerated at 36°F to 46°F (2°C to 8°C) in original package to protect from light.

Do not freeze or shake the vial.

The vial stopper is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions requiring corticosteroids or hormone replacement therapy, including, but not limited to:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath [[see Warnings and Precautions \(5.1\)](#)].
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding [[see Warnings and Precautions \(5.2\)](#)].

- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain [*see Warnings and Precautions (5.3)*].
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus [*see Warnings and Precautions (5.4)*].
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction [*see Warnings and Precautions (5.5)*].

Infusion-Related Reactions

Advise patients to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions [*see Warnings and Precautions (5.7)*].

Embryo-Fetal Toxicity

Advise females of reproductive potential that BAVENCIO can cause fetal harm. Instruct females of reproductive potential to use highly effective contraception during and for at least one month after the last dose of BAVENCIO [*see Warnings and Precautions (5.8) and Use in Specific Populations (8.1, 8.3)*].

Lactation

Advise nursing mothers not to breastfeed while taking BAVENCIO and for at least one month after the final dose [*see Use in Specific Populations (8.2)*].

Manufacturer:
EMD Serono, Inc.
Rockland, MA 02370
U.S.A.

Marketed by:
EMD Serono, Inc. and Pfizer Inc., NY, NY 10017

US License No: 1773

Product of Switzerland

BAVENCIO is a trademark of Merck KGaA,
Darmstadt, Germany

MEDICATION GUIDE
BAVENCIO® (buh-VEN-see-oh)
(avelumab)
injection

What is the most important information I should know about BAVENCIO?

BAVENCIO is a medicine that may treat your type of skin cancer (Merkel cell carcinoma) by working with your immune system. BAVENCIO can cause your immune system to attack normal organs and tissues in many areas of your body and can affect the way they work. These problems can sometimes become serious or life-threatening and can lead to death.

Call or see your healthcare provider right away if you get any symptoms of the following problems or these symptoms get worse:

Lung problems (pneumonitis). Signs and symptoms of pneumonitis may include:

- new or worsening cough
- shortness of breath
- chest pain

Liver problems (hepatitis). Signs and symptoms of hepatitis may include:

- yellowing of your skin or the whites of your eyes
- dark urine (tea colored)
- severe nausea or vomiting
- bleeding or bruising more easily than normal
- pain on the right side of your stomach area (abdomen)
- feeling less hungry than usual
- drowsiness

Intestinal problems (colitis). Signs and symptoms of colitis may include:

- diarrhea (loose stools) or more bowel movements than usual
- blood in your stools or dark, tarry, sticky stools
- severe stomach area (abdomen) pain or tenderness

Hormone gland problems (especially the thyroid, adrenal glands and pancreas). Signs and symptoms that your hormone glands are not working properly may include:

- rapid heart beat
- constipation
- increased sweating
- your voice gets deeper
- extreme tiredness
- very low blood pressure
- weight gain or weight loss
- urinating more often than usual
- feeling more hungry or thirsty than usual
- dizziness or fainting
- hair loss
- nausea or vomiting
- changes in mood or behavior, such as irritability or forgetfulness
- stomach area (abdomen) pain
- feeling cold

Kidney problems, including nephritis. Signs and symptoms of kidney problems may include:

- urinate less than usual
- swelling in your ankles
- blood in your urine
- loss of appetite

Problems in other organs. Signs and symptoms may include:

- severe muscle weakness
- tiredness, sleepiness
- severe or persistent muscle or joint pains
- swelling of the feet and legs
- chest pain and tightness
- dizziness or fainting
- trouble breathing
- fever, flu like symptoms
- skin rash, blisters or peeling
- changes in eyesight
- changes in heartbeat, such as beating fast, or seeming to skip a beat, or pounding sensation

Severe infusion reactions. Signs and symptoms of severe infusion reactions may include:

- chills or shaking
- low blood pressure
- hives
- fever
- flushing
- back pain
- shortness of breath or wheezing
- abdominal pain

Getting medical treatment right away may help keep these problems from becoming more serious.

Your healthcare provider will check you for these problems during your treatment with BAVENCIO. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may delay or

completely stop treatment with BAVENCIO if you have severe side effects.

What is BAVENCIO?

BAVENCIO is a prescription medicine used to treat a type of skin cancer called Merkel cell carcinoma. BAVENCIO may be used when your skin cancer has spread.

It is not known if BAVENCIO is safe and effective in children under the age of 12.

Before you receive BAVENCIO, tell your healthcare provider about all of your medical conditions, including if you:

- have immune system problems such as Crohn's disease or ulcerative colitis
- have had an organ transplant
- have lung or breathing problems
- have liver or kidney problems
- have diabetes
- are pregnant or plan to become pregnant. BAVENCIO can harm your unborn baby. If you are able to become pregnant, you should use an effective method of birth control during your treatment and for at least 1 month after the last dose of BAVENCIO.
- are breastfeeding or plan to breastfeed. It is not known if BAVENCIO passes into your breast milk. Do not breastfeed during treatment and for at least 1 month after the last dose of BAVENCIO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive BAVENCIO?

- Your healthcare provider will give you BAVENCIO into your vein through an intravenous (IV) line over 60 minutes.
- BAVENCIO is usually given every 2 weeks.
- Your healthcare provider will give you medicines before the first 4 infusions and subsequently as needed to help reduce infusion reactions.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will do blood tests to check you for certain side effects.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of BAVENCIO?

BAVENCIO can cause serious side effects, including:

- See “What is the most important information I should know about BAVENCIO?”

The most common side effects of BAVENCIO include:

- | | |
|------------------------|---|
| • feeling tired | • swelling in your hands, feet, or ankles |
| • muscle and bone pain | • decreased appetite |
| • diarrhea | • skin rash |
| • nausea | |

These are not all the possible side effects of BAVENCIO. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of BAVENCIO

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about BAVENCIO, talk with your healthcare provider. You can ask your healthcare provider for information about BAVENCIO that is written for health professionals.

What are the ingredients in BAVENCIO?

Active ingredient: avelumab

Inactive ingredients: D-mannitol, glacial acetic acid, polysorbate 20, sodium hydroxide, water for injection

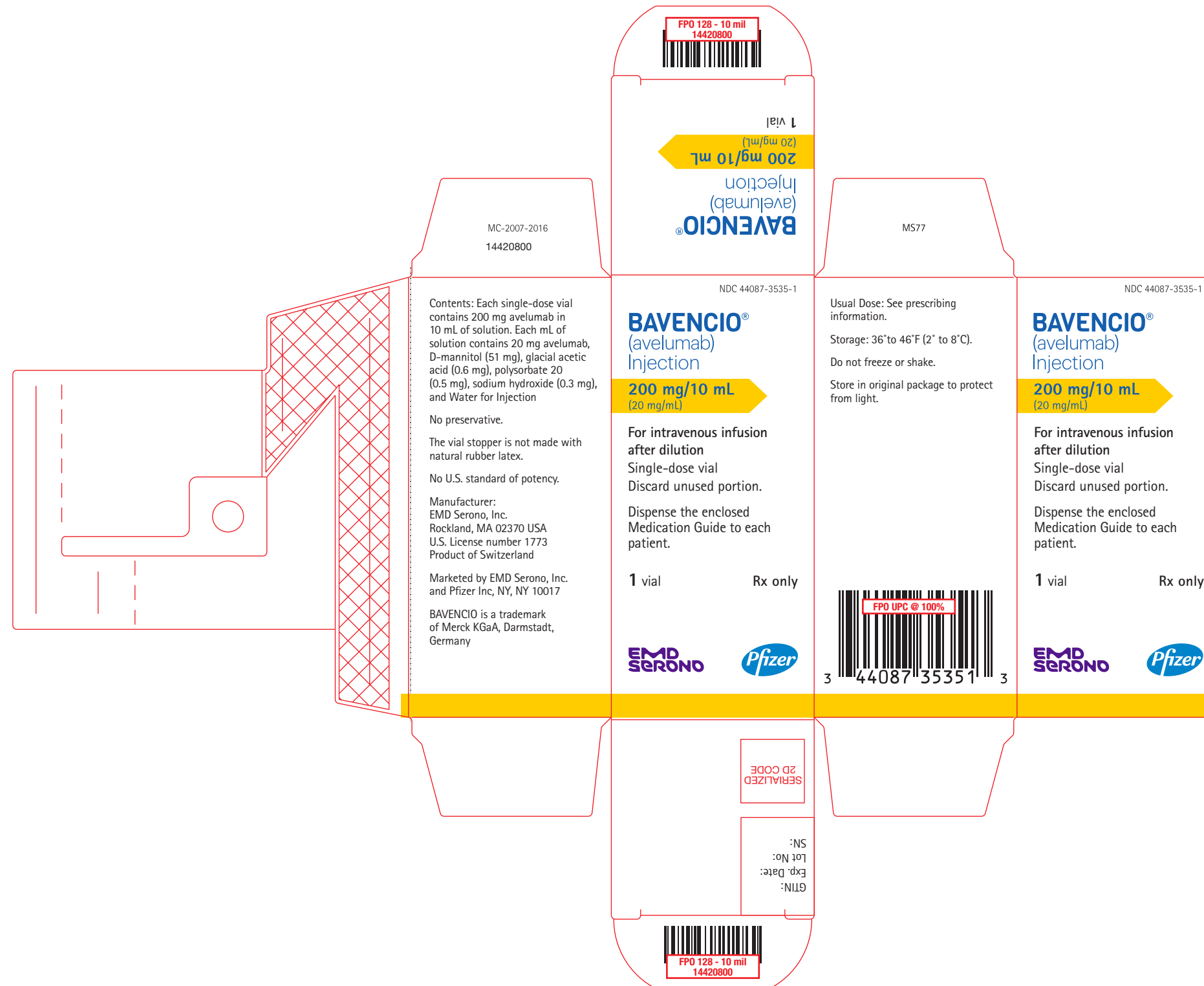
Manufacturer: EMD Serono, Inc. One Technology Place, Rockland, MA 02370 USA, U.S. License No. 1773.

Marketed by: EMD Serono, Inc. and Pfizer Inc., NY, NY 10017 USA.

BAVENCIO is a trademark of Merck KGaA, Darmstadt, Germany. For more information, call toll-free 1-844-826-8371 or go to www.bavencio.com.

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

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 100354408735353	NDC 44087-3535-1		Rx only	
	BAVENCIO®		EMD Serono, Inc.	
	(avelumab)			
	Injection			
200 mg/10 mL (20 mg/mL)		NO COPY		
For intravenous infusion after dilution Single-dose vial. Discard unused portion. Storage: 36° to 46°F (2° to 8°C). Protect from light.		Lot No: Exp:	IMPRINT AREA NO COPY	
		MC=2008=2016 14420700		

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/s/

RICHARD PAZDUR
03/23/2017