

BAVENCIO® (avelumab) is the **FIRST** and **ONLY** immunotherapy indicated for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy.¹



Instructions for the Epic® Electronic Health Record (EHR) System to Create or Update Order Sets With BAVENCIO® (avelumab)



Actor Portrayals



Avelumab is the only National Comprehensive Cancer Network® (NCCN®) **Category 1** and **Preferred** immunotherapy option for maintenance therapy for both cisplatin-eligible and cisplatin-ineligible patients with locally advanced or metastatic UC that has not progressed on first-line platinum-containing chemotherapy²

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

SELECT IMPORTANT SAFETY INFORMATION

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

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

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Background

This document is intended to provide medical groups with instructions to update locally advanced or metastatic UC order sets with BAVENCIO®, within the approved indication and consistent with the Prescribing Information. This document is not intended to provide any clinical advice or clinical recommendations, which are solely the responsibility of the healthcare professionals.

These instructions are specific to locally advanced or metastatic UC and to the Epic® EHR system and are not appropriate for other conditions, treatments, or therapeutic areas or for other EHR systems.



Considerations

The process outlined below is variable, and not all steps will apply to every medical group. Any steps or settings below that are not part of a medical group's standard process should be excluded or modified accordingly. Any questions should be directed to the appropriate service provider. The medical group is solely responsible for implementing, testing, monitoring, and ongoing operation of any EHR tools.

Please consult the most recent version of the BAVENCIO package insert for full medication details. The most recent version of the package insert can be found at <https://www.emdserono.com/us-en/pi/bavencio-pi.pdf>.

A new order set will be available once the order set optimization process is complete. If the original order set used to update or create the new order set includes BAVENCIO, confirm the original order set is retired or removed from the EHR production system according to the medical group's EHR governing principles.



3

Epic Beacon Protocol Instructions

Existing protocols may be used as a foundation for locally advanced or metastatic UC. Consider modifying a Beacon protocol as a starting template, while saving the original protocol.

There are 3 steps to update a Beacon protocol in the Epic EHR system.

1	Create 4 order groups to hold BAVENCIO 800 mg, the BAVENCIO Treatment Conditions (or Monitoring and Hold Parameters), BAVENCIO Warnings and Precautions, and BAVENCIO Premedications
2	Add the BAVENCIO package insert and resource links to the medication record
3	Add the Order Groups to the Beacon protocol

Step 1

General Instructions for Creating the Order Groups

- 1. Review the Regimen Category Order Group to confirm Medications are values in the category list
- 2. Select the Order Group Builder (Admin > Beacon Admin > Order Group Builder)
- 3. Create a new Order Group named "Medications"
- 4. Set the default category to Medications
- 5. Create the following 4 Order Groups:

Order Group 1: BAVENCIO

- 1. Right click in the empty field located on the bottom of the window
- 2. Select Add > Orders
- 3. Select BAVENCIO
- 4. Complete the BAVENCIO medication details (800 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity)

For the administration instructions, dose reductions, dose modifications and other information, refer to <https://www.emdserono.com/us-en/pi/bavencio-pi.pdf>

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Order Group 2: BAVENCIO Treatment Conditions

(Alternatively, consider Monitoring and Hold Parameters)

- 1. Review the Regimen Category Order Group to confirm Treatment Conditions (or Monitoring and Hold Parameters) is a value in the category list
- 2. Select the Order Group Builder (Admin > Beacon Admin > Order Group Builder)
- 3. Create a new Order Group named "BAVENCIO Treatment Conditions (or Monitoring and Hold Parameters)"
- 4. Set the default category to Treatment Conditions (or Monitoring and Hold Parameters)
- 5. Complete the following BAVENCIO Treatment Conditions (or Monitoring and Hold Parameters) Order Group:
 - a. Right click in the empty field located at the bottom of the window
 - b. Select Add > BAVENCIO Treatment Conditions (or Monitoring and Hold Parameters)
 - c. Enter a link to the PI "https://www.emdserono.com/us-en/pi/bavencio-pi.pdf" for the most recent information regarding Dose Modifications for Adverse Reactions (see *Table 1*)

Order Group 3: BAVENCIO Warnings and Precautions

- 1. Review the Regimen Category Order Group to confirm Warnings and Precautions is a value in the category list
- 2. Select the Order Group Builder (Admin > Beacon Admin > Order Group Builder)
- 3. Create a new Order Group named "BAVENCIO Warnings and Precautions"
- 4. Set the default category to Warnings and Precautions
- 5. Complete the following BAVENCIO Warnings and Precautions Order Group:
 - a. Right click in the empty field located at the bottom of the window
 - b. Select Add > BAVENCIO Warnings and Precautions
 - c. Enter a link to the PI "https://www.emdserono.com/us-en/pi/bavencio-pi.pdf" for the most recent information regarding Warnings and Precautions

Order Group 4: BAVENCIO Premedications

- 1. Select the Order Group Builder (Admin > Beacon Admin > Order Group Builder)
- 2. Create a new Order Group named "BAVENCIO Premedications"
- 3. Set the default category to Premedications
- 4. Complete the following BAVENCIO Premedications Order Group:
 - a. Right click in the empty field located on the bottom of the window
 - b. Select Add > Orders
 - c. Select the desired antihistamine and acetaminophen medications
 - d. Complete the medication details: E.g., "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"

Note: Consider an alternative Order Group, if desired, based on the medical group governing Beacon Regimen conventions.



Step 2

Add the BAVENCIO website links to the medication record

- 1. Log in to the Medication Master File (ERX) with authorized user credentials
- 2. Use the search feature in the Medication Master File to search and select the desired medication (BAVENCIO)
- 3. Select the Patient Medication References Screen and create 2 new rows
 - Row 1:** For Display Name, enter "BAVENCIO Package Insert"
In the Text field, enter "See URL for additional BAVENCIO dosing and administration information"
In the URL field, enter this hyperlink: "https://www.emdserono.com/us-en/pi/bavencio-pi.pdf"
 - Row 2:** For Display Name, enter "BAVENCIO Resources for Providers (HCPs) and Patients"
In the Text field, enter "See URL for additional BAVENCIO Resources for Providers (HCPs) and Patients such as a Treatment Guide, Patient Brochure, and Patient Savings Offers"
In the URL field, enter this hyperlink: "https://www.BAVENCIO.com"
- 4. Save the record
- 5. Release the record to production after satisfactory testing has been completed

Step 3

Add the Order Groups to the BAVENCIO locally advanced or metastatic UC Beacon protocol

The steps detail how to add the Order Groups (4 order groups) created in **Step 1** to an existing Beacon protocol to create a new BAVENCIO order group or order set for locally advanced or metastatic UC order set:

- 1. Click the Epic logo > Admin > Beacon Admin > Protocol Builder. Search for order sets using the search query "locally advanced or metastatic Urothelial Carcinoma (UC)." An existing BAVENCIO order set may be available to optimize
 - Note:** The existing order set will serve as a template for the new BAVENCIO order set only. If the original order set used to create or optimize the new BAVENCIO order set includes BAVENCIO, confirm it is retired or removed from the EHR production system according to the Customer's EHR governing principles.
- 2. Select the treatment regimen and add the newly created order group(s) from the previous Step 1 to the treatment regimen "800 mg every 2 weeks"
- 3. Add in the second Order Group created in Step 1 with the BAVENCIO Treatment Conditions (or Monitoring and Hold Parameters)
- 4. Add in the third Order Group created in Step 1 with the BAVENCIO Warnings and Precautions
- 5. Add in the fourth Order Group created in Step 1 with the BAVENCIO Premedications
- 6. Update the Beacon protocol description to "BAVENCIO for locally advanced or metastatic Urothelial Carcinoma (UC)"
- 7. Click Save
- 8. Release to production environment after satisfactory testing has been completed

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Notes

The medical groups shall be solely responsible for implementation, testing, and monitoring of the instructions to ensure proper orientation in each medical group's EHR system.

After completing the BAVENCIO order set optimization process, a new BAVENCIO order set will be available. If the original order set used to update or create the new BAVENCIO order set included BAVENCIO, confirm the original order set is retired or removed from the EHR production system according to the medical group's EHR governing principles.

Capabilities, functionality, and setup (customization) for each individual EHR system vary. EMD Serono is not responsible for revising the implementation instructions it provides to any medical group.

While EMD Serono tests its implementation instructions on multiple EHR systems, the instructions are not guaranteed to work for all available EHR systems and EMD Serono shall have no liability therefor.

While EHRs may assist providers in identifying appropriate patients for consideration of assessment and treatment, the decision and action should ultimately be made by a healthcare provider in consultation with the patient after a review of the patient's records to determine eligibility.

These instructions have not been designed to and are not tools and/or solutions for meeting Advancing Care Information and/or any other quality/accreditation requirement.

Reference to these EHRs is not intended to imply affiliation with or sponsorship of the EHR manufacturer and/or its affiliates.



INDICATIONS

BAVENCIO® (avelumab) is indicated for:

- The maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy
- The treatment of patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

IMPORTANT SAFETY INFORMATION

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

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

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

BAVENCIO can cause **immune-mediated pneumonitis**. Withhold BAVENCIO for Grade 2, and permanently discontinue for Grade 3 or Grade 4 pneumonitis. Immune-mediated pneumonitis occurred in 1.1% (21/1854) of patients, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%), and Grade 2 (0.6%) adverse reactions. Systemic corticosteroids were required in all (21/21) patients with pneumonitis.

BAVENCIO can cause **immune-mediated colitis**. The primary component of immune-mediated colitis consisted of diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade 4 colitis. Immune-mediated colitis occurred in 1.5% (27/1854) of patients, including Grade 3 (0.4%) and Grade 2 (0.8%) adverse reactions. Systemic corticosteroids were required in all (27/27) patients with colitis.

BAVENCIO can cause **hepatotoxicity and immune-mediated hepatitis**. Withhold or permanently discontinue BAVENCIO based on tumor involvement of the liver and severity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin elevation. Immune-mediated hepatitis occurred with BAVENCIO as a single agent in 1.1% (20/1854) of patients, including fatal (0.1%), Grade 3 (0.8%), and Grade 2 (0.2%) adverse reactions. Systemic corticosteroids were required in all (20/20) patients with hepatitis.

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IMPORTANT SAFETY INFORMATION (continued)

BAVENCIO can cause primary or secondary **immune-mediated adrenal insufficiency**. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated adrenal insufficiency occurred in 0.6% (11/1854) of patients, including Grade 3 (0.1%) and Grade 2 (0.4%) adverse reactions. Systemic corticosteroids were required in all (11/11) patients with adrenal insufficiency.

BAVENCIO can cause **immune-mediated hypophysitis**. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated pituitary disorders occurred in 0.1% (1/1854) of patients, which was a Grade 2 (0.1%) adverse reaction.

BAVENCIO can cause **immune-mediated thyroid disorders**. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Thyroiditis occurred in 0.2% (4/1854) of patients, including Grade 2 (0.1%) adverse reactions. Hyperthyroidism occurred in 0.4% (8/1854) of patients, including Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in 25% (2/8) of patients with hyperthyroidism. Hypothyroidism occurred in 5% (97/1854) of patients, including Grade 3 (0.2%) and Grade 2 (3.6%) adverse reactions. Systemic corticosteroids were required in 6% (6/97) of patients with hypothyroidism.

BAVENCIO can cause **immune-mediated type I diabetes mellitus**, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated type I diabetes mellitus occurred in 0.2% (3/1854) of patients, including Grade 3 (0.2%) adverse reactions.

BAVENCIO can cause **immune-mediated nephritis with renal dysfunction**. Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade 4 increased blood creatinine. Immune-mediated nephritis with renal dysfunction occurred in 0.1% (2/1854) of patients, including Grade 3 (0.1%) and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in all (2/2) patients with nephritis with renal dysfunction.

BAVENCIO can cause **immune-mediated dermatologic adverse reactions**, including rash or dermatitis. Exfoliative dermatitis including Stevens Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold BAVENCIO for suspected and permanently discontinue for confirmed SJS, TEN, or DRESS. Immune-mediated dermatologic adverse reactions occurred in 6% (108/1854) of patients, including Grade 3 (0.1%) and Grade 2 (1.9%) adverse reactions. Systemic corticosteroids were required in 25% (27/108) of patients with dermatologic adverse reactions.

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

BAVENCIO can cause severe or life-threatening **infusion-related reactions**. Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent infusions based upon clinical

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IMPORTANT SAFETY INFORMATION (continued)

judgment and presence/severity of prior infusion reactions. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for Grade 1 or Grade 2 infusion-related reactions. Permanently discontinue BAVENCIO for Grade 3 or Grade 4 infusion-related reactions. Infusion-related reactions occurred in 26% of patients, including three (0.2%) Grade 4 and ten (0.5%) Grade 3 infusion-related reactions. Eleven (85%) of the 13 patients with Grade ≥ 3 reactions were treated with intravenous corticosteroids.

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

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

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

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

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

Please see full Prescribing Information [here](#).

References: 1. Bavelio [prescribing information]. Rockland, MA: EMD Serono, Inc. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer V.3.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed August 16, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.



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