**CLINICAL GUIDELINES FOR MEDICAL NECESSITY**

**MEDICAL POLICY**

# Avelumab (Bavencio®)

Version: 1.0

**EFFECTIVE DATE: 1/1/2024**

NantHealth® | Eviti®

## Please note the following:

## Avelumab (Bavencio®)

**Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.**

**Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.**

## Avelumab (Bavencio): Discussion

Avelumab is a programmed death ligand-1 blocking antibody. 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.[1]

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.[1]

Avelumab use 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 treatment with avelumab; however, immune-mediated adverse reactions can occur after discontinuation of avelumab.[1]

Avelumab is approved by the Food and Drug Administration (FDA) for the treatment of the following disease:

**Merkel Cell Carcinoma (MCC)**
Adults and pediatric patients 12 years and older with metastatic MCC. This indication is approved under accelerated approval based on the tumor response rate and the duration of response.

**Urothelial Carcinoma (UC)**

1. Maintenance treatment of patients with locally advanced or metastatic UC that has not progressed with first-line platinum-containing chemotherapy; OR

2. 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.

**Renal Cell Carcinoma (RCC)**
First-line treatment, in combination with axitinib, for patients with advanced RCC. [1]

The National Comprehensive Cancer Network (NCCN) endorses avelumab for the following cancer types: urothelial cancer of the bladder, urothelial cancer of the urethra, urothelial cancer of the upper genitourinary tract, urothelial cancer of the prostate, gestational trophoblastic neoplasia, kidney, Merkel cell carcinoma, and uterine neoplasms.[2,3,4,5,6]

Immune-mediated adverse reactions (IMARs) may occur. The treatment with inhibitors for the checkpoint proteins can result in adverse reactions that present similarly to other conditions. These immune-mediated adverse reactions (IMARs) are most commonly gastrointestinal, respiratory, endocrine, or dermatologic. More rarely, neurologic, ocular, cardiovascular, hematologic, and renal IMARs can occur. The median time to onset of IMARs with anti-PD-1/PD-L1 antibodies is typically between 1 and 6 months; however, IMARs again may present as late as 41 months after treatment initiation. For ipilimumab (anti-CTLA-4), dermatologic IMARs typically present after 2–3 weeks of treatment, while GI and hepatic IMARs appear after 6–7 weeks and some endocrinopathies can appear 9 weeks or later after immunotherapy. High-dose steroids are often used as a first attempt at symptom control, with long tapers occurring over at least 4 weeks. Early recognition and prompt, appropriate treatment of IMARs arising from ICIs increase the likelihood of resolving IMARs.[8]

## Avelumab: Definitions

- **Deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H)** – when the microsatellite DNA segments in cancer cells show changes (mutations), this indicates that the tumor cells are deficient in the repair of the mismatch errors. These cancers have microsatellite instability (also called MSI-High, MSI-H, or mismatch repair deficiency, dMMR).
- **Food and Drug Administration (FDA)** – The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- **Immune checkpoint inhibitors (ICIs) -** Immunotherapy drugs called immune checkpoint inhibitors work by blocking checkpoint proteins from binding with their partner proteins. This prevents the "off" signal from being sent, allowing the T cells to kill cancer cells. One such drug acts against a checkpoint protein called CTLA-4. Other immune checkpoint inhibitors act against a checkpoint protein called PD-1 or its partner protein PD-L1.[7]
- **Immune-mediated adverse reactions (IMARs) -** Immune checkpoint proteins, such as cytotoxic T-lymphocyte antigen-4 and programmed death-1, are part of the normal immune system and regulate immune activation.
- **Programmed cell death protein 1 (PD-1)/Programmed cell death-ligand 1 (PD-L1) –** Checkpoint proteins, such as PD-L1 on tumor cells and PD-1 on T cells, help keep

immune responses in check. The binding of PD-L1 to PD-1 keeps T cells from killing tumor cells in the body. Blocking the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1) allows the T cells to kill tumor cells.[7]

- **National Comprehensive Cancer Network (NCCN) -** An alliance of 32 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.

## Avelumab: Policy

Avelumab will be considered for coverage when the following criteria are met:

1. Individuals receiving PD-1 or PD-L1 therapy should not be receiving therapy for an autoimmune disease or chronic condition with a systemic immunosuppressant.
2. Individuals receiving Avelumab should not have experienced progression or unacceptable toxicity on prior therapy with a PD-1 or PD-L1 agent.

### Urothelial Carcinoma (UC)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Locally advanced or metastatic UC in one of the following:
    a) Disease progression during or following platinum-containing chemotherapy
    b) Disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. [1]

### Urothelial Cancer of the Bladder

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Used as single-agent maintenance therapy if there is no progression on first-line platinum-containing chemotherapy with:
    a) Gemcitabine and cisplatin
    b) DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, cisplatin)
    c) Gemcitabine and carboplatin; OR
4. Used as second-line systemic therapy post-platinum or other chemotherapy as a single agent for:
    a) Stage II (cT2, N0) disease or stage IIIA (cT3, N0; cT4a, N0; cT1-4a, N1) disease if the tumor is present following reassessment of tumor status 2-3 months after primary treatment with concurrent bladder-preserving chemoradiotherapy and maximal transurethral resection of bladder tumor (TURBT)
    b) Stage IIIB (cT1-4a, N2,3) disease following partial response or progression after primary treatment with downstaging systemic therapy or concurrent

chemoradiotherapy
c) Stage IVA (cT4b, any N, M0) disease if the tumor is present following reassessment of tumor status after primary treatment with first-line systemic therapy or concurrent chemoradiotherapy
d) Stage IVA (any T, any N, M1a) disease if the disease is stable or progression following the reassessment of the tumor status after the primary treatment with first-line systemic therapy
e) Metastatic stage IVB (any T, and N, M1b) disease
f) Muscle invasive local recurrence or persistent disease in a preserved bladder treated with curative intent
g) Metastatic or local recurrence post cystectomy treated with curative intent

**Urothelial Cancer of the Urethra**

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Used as single-agent maintenance therapy if there is no progression on first-line platinum-containing chemotherapy with:
    a) Gemcitabine and either cisplatin or carboplatin
    b) DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, cisplatin); OR
4. Used as a single-agent for recurrent or metastatic disease as second-line systemic therapy post-platinum or other chemotherapy

**Urothelial Cancer of the Renal Pelvis and Ureter**

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Used as single-agent maintenance therapy if there is no progression on first-line platinum-containing chemotherapy with:
    a) Gemcitabine and either cisplatin or carboplatin
    b) DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, cisplatin); OR
4. Therapy for metastatic disease as a single agent for second-line systemic therapy post-platinum or other chemotherapy

**Urothelial Cancer of the Prostate**

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Used as single-agent maintenance therapy if there is no progression on first-line platinum-containing chemotherapy with:
    a) Gemcitabine and either cisplatin or carboplatin
    b) DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, cisplatin); OR
4. Therapy for metastatic disease as a single agent for second-line systemic therapy post-platinum or other chemotherapy [2]

**Gestational Trophoblastic Neoplasia**

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Useful in certain circumstances as single-agent therapy for multiagent chemotherapy-resistant:
    a) High-risk disease; OR
    b) Recurrent or progressive intermediate trophoblastic tumor (placental site trophoblastic tumor or epithelioid trophoblastic tumor) [3]

**Kidney Cancer (Clear Cell)**

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Used in combination with axitinib for relapse or stage IV disease as first-line therapy [4]

**Merkel Cell Carcinoma**

1. At least 12 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. May be considered as a single-agent treatment for M1 disseminated disease with or without surgery and/or radiation therapy [5]

**Uterine Neoplasms**

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Second-line or subsequent therapy as a single agent for recurrent microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors:
    a) May be considered for isolated metastases
    b) For disseminated metastases with or without sequential palliative external beam radiation therapy (ERBT)
    c) With sequential ERBT and with or without brachytherapy for locoregional recurrence in patients with no prior radiation therapy (RT) to the site of recurrence, or previous brachytherapy only
    d) After surgical exploration, with sequential ERBT for locoregional recurrence in patients with disease confined to the vagina or paravaginal soft tissue, OR in pelvic, para-aortic, or common iliac lymph nodes
    e) After surgical exploration, with or without sequential ERBT for locoregional recurrence in patients with upper abdominal or peritoneal disease
    f) With or without sequential palliative ERBT or brachytherapy for locoregional recurrence in patients who have received prior ERBT to the site of recurrence [6]

**Note:** Coverage of avelumab will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a category 1, 2A, or 2B recommendation OR when all criteria are met.

## Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

## Avelumab: References


1. Bavencio® (Avelumab) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761049s013lbl.pdf. Accessed May 17, 2023.
2. National Comprehensive Cancer Network Guidelines. Bladder Cancer (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed May 17, 2023.
3. National Comprehensive Cancer Network Guidelines. Gestational Trophoblastic Neoplasia (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/gtn.pdf. Accessed May 17, 2023.
4. National Comprehensive Cancer Network Guidelines. Kidney Cancer (Version 4.2023). https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed May 17, 2023.
5. National Comprehensive Cancer Network Guidelines. Merkel Cell Carcinoma (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/mcc.pdf. Accessed May 18, 2023.
6. National Comprehensive Cancer Network Guidelines. Uterine Neoplasms (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed May 18, 2023.
7. National Cancer Institute. Immune Checkpoint Inhibitors; April 7, 2022. https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/checkpoint-inhibitors Accessed May 24, 2023.
8. Emerg Med J 2019: Challenge of Immune-Mediated Adverse Reactions in the Emergency Department;36:369-77. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6582806/pdf/emermed-2018-208206.pdf. Accessed May 31, 2023.


## Avelumab: Coding (CPT®, ICD 10 and HCPCS*)

*Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

| CODE | DESCRIPTION |
|---|---|
| C4A.9 | Merkel cell carcinoma |
| C55 | Malignant neoplasm of the uterus, part unspecified |

| | |
|---|---|
| C64.9 | Malignant neoplasm of the kidney |
| C67.0 | Urothelial cancer of the bladder |
| C67.9 | Urothelial cancer of the renal pelvis and ureter |
| J9023 | Avelumab (Bavencio®) |
| O01.9 | Gestational trophoblastic neoplasia |

## Avelumab: Revision and Review History

| No. | Description | Date(s) |
|---|---|---|
| 1 | Original Effective Date: | 1/1/2024 |
| 2 | Policy Review Dates: | 6/13/2023 |
| 3 | Policy Revision Dates: | |
| 4 | Department Owner: | Medical Affairs |
| 5 | NH Advisory Committee Approval Dates: | 7/20/2023 |
| 6 | Revision Changes: | |