Bavencio® (avelumab)
(Intravenous)

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I. Length of Authorization

Coverage will be provided for six months and may be renewed.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Bavencio 200 mg single-use vial: 4 vials per 14 days

B. Max Units (per dose and over time) [HCPCS Unit]:

- 80 billable units every 14 days (all indications)

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

Universal Criteria

- Patient has not received previous therapy with a programmed death (PD-1/PD-L1)-directed therapy (e.g., nivolumab, pembrolizumab, atezolizumab, durvalumab, cemiplimab, etc.), unless otherwise specified; AND

Merkel Cell Carcinoma (MCC) † Φ [1,2,4,5,2e,3e]

- Patient is at least 12 years of age; AND
- Used as a single agent; AND
- Patient has distant metastatic disease

Bladder Cancer/Urothelial Carcinoma † [1,4,6,8]

- Patient is at least 18 years of age; AND
- Used as a single agent; AND

- Used as subsequent therapy after previous platinum treatment*; **AND**
- Patient has a diagnosis of one of the following:
  - Locally advanced or metastatic urothelial carcinoma; **OR**
  - Local muscle invasive bladder cancer recurrence or persistent disease in a preserved bladder; **OR**
  - Local or metastatic bladder cancer recurrence post-cystectomy; **OR**
  - Metastatic upper genitourinary (GU) tract tumors; **OR**
  - Metastatic urothelial carcinoma of the prostate; **OR**
  - Recurrent or metastatic primary carcinoma of the urethra; **AND**
    - Patient does not have recurrence of stage T3-4 disease or palpable inguinal lymph nodes; **OR**
- Used as first-line maintenance treatment; **AND**
  - Patient has locally advanced or metastatic urothelial carcinoma (inclusive of the bladder, upper GU, urethra, and/or prostate); **AND**
  - Patient has not progressed with first-line platinum-containing chemotherapy; **AND**
  - Treatment will be initiated within 4 – 10 weeks after the last dose of chemotherapy

Note:

– *If platinum treatment occurred greater than 12 months ago, the patient should be re-treated with platinum-based therapy if the patient is still platinum eligible (see below for cisplatin- or carboplatin-ineligible comorbidities).*

- *Cisplatin-ineligible comorbidities may include the following: GFR < 60 mL/min, PS ≥ 2, hearing loss of ≥ 25 decibels (dB) at two contiguous frequencies, or grades ≥ 2 peripheral neuropathy, etc.. Carboplatin may be substituted for cisplatin particularly in those patients with a GFR <60 mL/min or a PS of 2.*
- *Carboplatin-ineligible comorbidities may include the following: GFR < 30 mL/min, PS ≥ 3, grade ≥ 3 peripheral neuropathy, or NYHA class ≥ 3, etc.*

Renal Cell Carcinoma † [1,4,9]

- Patient is at least 18 years of age; **AND**
- Used in combination with axitinib; **AND**
- Used as first line therapy; **AND**
  - Used for the treatment of advanced disease with clear cell histology; **OR**
  - Used for relapsed or metastatic disease with clear cell histology

Gestational Trophoblastic Neoplasia ‡ [4,13,15e]

- Patient is at least 18 years of age; **AND**
- Used as single-agent therapy for patients resistant to single-agent chemotherapy

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

IV. Renewal Criteria[1,2,8,9]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet the universal and other indication-specific relevant criteria identified in section III; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe infusion reactions, hepatotoxicity, immune-mediated adverse reactions (e.g., pneumonitis, hepatitis, colitis, endocrinopathies, nephritis and renal dysfunction, myocarditis, pancreatitis, myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome, systemic inflammatory responses, etc.), major adverse cardiovascular events (MACE) when used in combination with axitinib, complications of allogeneic HSCT, etc.

V. Dosage/Administration[1,2,8,9]

Indication	Dose
All indications	800 mg via intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.
Dosing should be calculated using actual body weight and not flat dosing (as applicable) based on the following: **Weight > 60 kg**: • Standard dose 800 mg IV every 2 weeks **Weight is ≤ 60kg**: • Use 600 mg IV every 2 weeks *Note: This information is not meant to replace clinical decision making when initiating or modifying medication therapy and should only be used as a guide. Patient-specific variables should be taken into account.*	

VI. Billing Code/Availability Information

HCPCS Code:

- J9023 – Injection, avelumab, 10 mg; 1 billable unit = 10 mg

NDC:

- Bavencio 200 mg/10 mL single-dose vial: 44087-3535-xx

VII. References (STANDARD)

1. Bavencio [package insert]. New York, NY; EMD Serono, Inc; November 2020. Accessed March 2021.
2. Kaufman HL, Russell J, Hamid O, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol. 2016 Oct;17(10):1374-1385.
3. Novakovic AM, Wilkins JJ, Dai H, et al. Changing body weight-based dosing to a flat dose for avelumab in metastatic Merkel cell and advanced urothelial carcinoma. Clin Pharmacol Ther. 2019 Sep 25.
4. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) avelumab. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2021.
5. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Merkel Cell Carcinoma, Version 1.2021 National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2021.
6. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Bladder Cancer, Version 6.2020. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2021.
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13. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Gestational Trophoblastic Neoplasia. Version 1.2021. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2021.

VIII. References (ENHANCED)

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Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C4A.0	Merkel cell carcinoma of lip

ICD-10	ICD-10 Description
C4A.10	Merkel cell carcinoma of eyelid, including canthus
C4A.111	Merkel cell carcinoma of right upper eyelid, including canthus
C4A.112	Merkel cell carcinoma of right lower eyelid, including canthus
C4A.121	Merkel cell carcinoma of left upper eyelid, including canthus
C4A.122	Merkel cell carcinoma of left lower eyelid, including canthus
C4A.20	Merkel cell carcinoma of unspecified ear and external auricular canal
C4A.21	Merkel cell carcinoma of right ear and external auricular canal
C4A.22	Merkel cell carcinoma of left ear and external auricular canal
C4A.30	Merkel cell carcinoma of unspecified part of face
C4A.31	Merkel cell carcinoma of nose
C4A.39	Merkel cell carcinoma of other parts of face
C4A.4	Merkel cell carcinoma of scalp and neck
C4A.51	Merkel cell carcinoma of anal skin
C4A.52	Merkel cell carcinoma of skin of breast
C4A.59	Merkel cell carcinoma of other part of trunk
C4A.60	Merkel cell carcinoma of unspecified upper limb, including shoulder
C4A.61	Merkel cell carcinoma of right upper limb, including shoulder
C4A.62	Merkel cell carcinoma of left upper limb, including shoulder
C4A.70	Merkel cell carcinoma of unspecified lower limb, including hip
C4A.71	Merkel cell carcinoma of right lower limb, including hip
C4A.72	Merkel cell carcinoma of left lower limb, including hip
C4A.8	Merkel cell carcinoma of overlapping sites
C4A.9	Merkel cell carcinoma, unspecified
C58	Malignant neoplasm of placenta
C61	Malignant neoplasm of prostate
C64.1	Malignant neoplasm of right kidney, except renal pelvis
C64.2	Malignant neoplasm of left kidney, except renal pelvis
C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C65.1	Malignant neoplasm of right renal pelvis
C65.2	Malignant neoplasm of left renal pelvis
C65.9	Malignant neoplasm of unspecified renal pelvis
C66.1	Malignant neoplasm of right ureter
C66.2	Malignant neoplasm of left ureter
C66.9	Malignant neoplasm of unspecified ureter
C67.0	Malignant neoplasm of trigone of bladder
C67.1	Malignant neoplasm of dome of bladder
C67.2	Malignant neoplasm of lateral wall of bladder
C67.3	Malignant neoplasm of anterior wall of bladder

ICD-10	ICD-10 Description
C67.4	Malignant neoplasm of posterior wall of bladder
C67.5	Malignant neoplasm of bladder neck
C67.6	Malignant neoplasm of ureteric orifice
C67.7	Malignant neoplasm of urachus
C67.8	Malignant neoplasm of overlapping sites of bladder
C67.9	Malignant neoplasm of bladder, unspecified
C68.0	Malignant neoplasm of urethra
C7B.1	Secondary Merkel cell carcinoma
D09.0	Carcinoma in situ of bladder
D39.2	Neoplasm of uncertain behavior of placenta
Z85.51	Personal history of malignant neoplasm of bladder
Z85.59	Personal history of malignant neoplasm of other urinary tract organ
Z85.821	Personal history of Merkel cell carcinoma

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; BOR = best overall response; RT = radiation; mMCC = metastatic Merkel cell carcinoma

Merkel Cell Carcinoma (MCC)

Metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Avelumab	2A preferred	Yes	Phase 2 (JAVELIN Merkel 200, part B), multicenter, international, single-arm, open-label	N/A	ORR	First-line for distant metastatic disease	• First-line avelumab monotherapy in patients with mMCC was associated with high response rates and a manageable safety profile
Avelumab	2A preferred	Yes	Phase 2 (JAVELIN Merkel 200, part A), multicenter, international, single-arm, open-label	N/A	ORR	Second-line or later for distant metastatic disease	• Avelumab demonstrated durable responses and promising survival outcomes in patients with mMCC whose disease had progressed after chemotherapy
Pembrolizumab	2A preferred	No	Phase 2 (NCT02267603), single-arm, multicenter	N/A	ORR	First-line for distant metastatic or recurrent locoregional disease	• First-line therapy with pembrolizumab in patients with advanced MCC was associated with an objective response rate of 56%

Nivolumab	2A preferred	No	Phase 1/2 (Checkmate 358)	N/A	ORR	First- to third-line	• Nivolumab induced durable tumor regression with an ORR of 68%

Urothelial Carcinoma (Bladder Cancer, Upper Genitourinary Tract Tumors, Urothelial Carcinoma of the Prostate, Primary Carcinoma of the Urethra)

Locally advanced or metastatic disease refractory to platinum-containing chemotherapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	1 preferred	Yes	Phase 3 (KEYNOTE-045), open-label, randomized	Investigator's choice: paclitaxel, docetaxel, or vinflunine	OS PFS	Second-line or later (platinum-refractory disease)	• Pembrolizumab was associated with significantly longer overall survival (by approximately 3 months) compared to chemotherapy
Avelumab	2A preferred	Yes	Phase 1b	N/A	Safety ORR (secondary end-point)	Second-line or later (platinum refractory, carcinoma of the renal pelvis, ureter, urinary bladder, or urethra)	• Avelumab was well tolerated and associated with an ORR of 18.2%
Avelumab	2A preferred	Yes	Pooled analysis from 2 expansion cohorts of a Phase 1 trial (JAVELIN Solid Tumor)	N/A	ORR	Second-line or later (platinum refractory, general urothelial carcinoma) or within 12 months of platinum-containing neoadjuvant or	• Avelumab showed antitumor activity in the treatment of patients with platinum-refractory metastatic urothelial carcinoma

						adjuvant chemotherapy	
Atezolizumab	2A preferred	Yes	Phase 2 (NCT02108652), two-cohort, multicenter	N/A	ORR	Cohort 2: Second-line or later (platinum-refractory disease)	• Atezolizumab showed durable activity and good tolerability in patients with metastatic urothelial carcinoma
Nivolumab	2A preferred	Yes	Phase 2 (CheckMate 275), single-arm, multicenter	N/A	ORR	Second-line or later (platinum refractory)	• Nivolumab monotherapy demonstrated an ORR of 19.6%. Benefit was observed irrespective of PD-L1 expression.
Erdafitinib	2A alternative preferred (post-platinum, FGFR3 or FGFR2 genetic alterations)	Yes (for FGFR3 or FGFR2 genetic alterations)	Phase 2 (BLC2001), open-label	N/A	ORR	After ≥ 1 line of prior chemo or ≤ 12 mon of [neo]adjuvant chemo, or were cisplatin ineligible, chemo naïve	• Treatment with erdafitinib yielded an ORR of 42% and was tolerable in patients with chemo-refractory metastatic urothelial carcinoma and FGFR generic alterations.

Renal Cell Carcinoma

First-line therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Avelumab + axitinib	2A other	Yes	Phase 3 (JAVELIN Renal 101), randomized,	Sunitinib	PFS and OS among patients with PD-L1-positive tumors	Untreated advanced clear cell RCC regardless of PD-L1 expression	• PFS was significantly longer with avelumab plus axitinib than with sunitinib among patients who received these agents as first-line treatment for advanced clear cell renal-cell carcinoma

			multi-center, open-label				
Pembrolizumab + axitinib	2A preferred for favorable risk 1 preferred for poor/ intermediate risk	Yes	Phase 3 (KEYNOTE-426), randomized, open-label	Sunitinib	PFS OS	Untreated advanced clear cell RCC	• Among patients with previously untreated advanced renal-cell carcinoma, treatment with pembrolizumab plus axitinib resulted in significantly longer overall survival and progression-free survival, as well as a higher objective response rate, than treatment with sunitinib
Nivolumab + ipilimumab	2A other for favorable risk 1 preferred for poor/ intermediate risk	Yes for intermediate/ poor-risk	Phase 3 (CheckMate 214), randomized, open-label, multi-center	Sunitinib	ORR PFS OS	First-line	• Overall survival and objective response rates were significantly higher with nivolumab plus ipilimumab than with sunitinib among intermediate- and poor-risk patients with previously untreated advanced renal-cell carcinoma.

Gestational Trophoblastic Neoplasia

Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Avelumab	2A	No	Phase 2 (TROPHIMMUN), cohort A	N/A	Rate of hCG normalization	Patients resistant to single-agent chemotherapy (previous therapy included methotrexate or dactinomycin)	• In patients with gestational trophoblastic tumors resistant to single-agent chemotherapy, treatment with avelumab resulted in successful hCG normalization in 8 of 15 patients (53%).

Pembrolizumab	2A	No	Case series	N/A	--------	Second-line or subsequent therapy	• Pembrolizumab demonstrated durable responses in 3 out of 4 patients with resistant GTN.
Nivolumab	2A	No	No clinical literature to support use.				