Effective November 1, 2018, refer to Palmetto Article A56141

BlueCross BlueShield of Alabama

"Unless otherwise noted, coverage for specific indications is effective the date of the FDA approval of that indication."
"Please check Approved by Governing Bodies for FDA approval date."

Name of Blue Advantage Policy:
Bavencio® (avelumab)

Policy #: 672
Category: Pharmacy
Effective Date: August 1, 2017
Latest Review Date: October 2018

Background:
Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Avelumab belongs to a group of cancer drugs called checkpoint inhibitors. They act by stimulating the immune system to destroy tumor cells; it specifically acts to block PD-L1. 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.

Policy:

Effective for dates of service on or after November 1, 2018 refer to Palmetto Article A56141

Effective for dates of service on and after August 1, 2017 and prior to November 1, 2018:
Blue Advantage will treat **Bavencio® (avelumab)** as a **covered benefit** for the treatment of **metastatic Merkel cell carcinoma** when **all** of the following criteria are met:

A. Individual is 12 years of age or older; **and**
B. Individual has a current Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; **and**
C. Individual has not received treatment with another PD-1 agent (for example, nivolumab or pembrolizumab); **and**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant.

Blue Advantage will treat **Bavencio® (avelumab)** as a **covered benefit** when used as **a single agent** for the treatment of **locally advanced or metastatic urothelial carcinoma** when **all** of the following criteria are met:

A. Have disease progression during or following platinum-containing chemotherapy; **OR**
B. Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; **and**
C. Individual has a current ECOG performance status of 0-2; **and**
D. Individual has not received treatment with another PD-1 agent (for example, nivolumab or pembrolizumab); **and**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most

appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Merkel Cell Carcinoma (MCC)

Skin cancer is the most common type of cancer in the United States. Merkel cell carcinoma is a rare, aggressive type of skin cancer. It is considered to be aggressive because it can grow quickly and spread and it returns after treatment. According to the American Cancer Society (2018), it is estimated there are 1500 new cases of Merkel cell carcinoma diagnosed each year with an overall 5-year survival rate of 30% to 64%. A major risk factor for Merkel cell carcinoma is a history of extensive sun exposure, particularly to the head and neck. Clinical suspicion of Merkel cell carcinoma is rare as the primary tumor lacks distinguishing characteristics. The initial workup of a suspicious lesion starts with an exam of the skin and lymph nodes following a biopsy. The primary treatment for Merkel cell carcinoma is surgery. The literature for the benefits of radiation therapy has been mixed and the literature is sparse on the use of chemotherapy for Merkel cell carcinoma.

The FDA accelerated approval of avelumab was based on a 2016 phase II open-label, single-arm, multicenter trial by Kaufman and colleagues which evaluated the safety and efficacy of avelumab. The participants (n=88) had histologically confirmed metastatic Merkel cell carcinoma (stage IV) and had already received chemotherapy. Participant eligibility included ECOG status of 0 or 1, measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, adequate hematological, hepatic, and renal function, and immune-competent status. Exclusion criteria of the study participants included those with autoimmune disease; medical conditions which required systemic immunosuppression; prior transplant of organs or allogeneic stem cell; prior treatment with anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibodies; metastases of the central nervous system; infection with human immunodeficiency virus, hepatitis B or C; or ECOG performance score greater than or equal to 2. The primary endpoint was an objective response (either complete response or partial response) which was assessed by RECIST version 1.1. Avelumab was given intravenously every 2 weeks. The median follow-up was 10.4 months. An objective response was achieved in 28 participants (31.8% [95.9% confidence interval (CI) 21.9-43.1]). Of those participants with an objective response, 8 had complete response and 20 had partial responses. At the time of analysis, responses were ongoing in 23 of 28 subjects. Grade 3 adverse events occurred in 4 participants (lymphopenia, blood creatinine phosphokinase increase, aminotransferase increase, and blood cholesterol increase). Serious adverse events were reported in 5 participants (enterocolitis, infusion-related reaction, aminotransferases increased, chondrocalcinosis, synovitis, and interstitial nephritis). There were no grade 4 adverse events or treatment-related deaths reported.

Urothelial Carcinoma (UC)

An estimated 81,190 new cases of urinary bladder cancer will be diagnosed in the United States in 2018 with approximately 17,240 deaths occurring during this same period. Bladder cancer, the sixth most common cancer in the United States, is rarely diagnosed in individuals younger than 40 years of age.

The FDA approval was based on the JAVELIN solid tumor trial, an open-label, single-arm study of avelumab in 242 participants who had metastatic or locally advanced urothelial carcinoma. The participants had disease progression on or after platinum-containing chemotherapy or had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. The participants received avelumab every 2 weeks until signs of progression or unacceptable toxicity. Response to tumor was assessed every 6 weeks. Efficacy outcome measures included overall response rate using RECIST v1.1 and duration of response was evaluated for a minimum of both 13 weeks and 6 months. A total of 226 participants had a minimum of 13 weeks of follow-up and 161 participants had a minimum of 6 months of follow-up. At the 13 week follow-up, 30 participants had an overall response, 9 with complete response and 21 with partial response. At the 6 month follow-up, 26 participants had an overall response, 9 with complete response and 17 with partial response. At both follow-up times (13 weeks and 6 months), 22 participants had an ongoing response of 6 months or longer and 4 participants had ongoing responses of 12 months or longer.

In a phase Ib expansion trial, Apolo and colleagues (2017) used 44 individuals with metastatic urothelial carcinoma from the JAVELIN study to report on a dose-expansion study. The included participants had metastatic urothelial carcinoma of the renal pelvis, ureter, urinary bladder, or urethra. Eligible participants had relapsed, refractory, or progressive disease as measured by RECIST v1.1 after at least one prior line of treatment. The primary outcome was safety and tolerability of avelumab with a primary endpoint of occurrence of dose-limiting toxicities during the first 3 weeks of treatment. Secondary endpoints included overall response, duration of response, progression-free survival, overall survival, and evaluation of PD-L1 expression. Participants were followed for a median of 16.5 months. Participants received avelumab every 2 weeks with a median of 7 doses and a median duration of 14.1 weeks. All participants had an adverse event with 29 participants having a treatment-related adverse event. The most common treatment-related adverse events were fatigue (n=9), infusion-related reaction (n=9), asthenia (n=5), and nausea (n=5). Complete response was found in 5 participants, partial response in 3 participants, stable disease in 15 participants, progressive disease in 15 participants and 6 participants were not available for evaluation. The median progression-free survival was 11.6 weeks (95% CI, 6.1-17.4). Median overall survival was 13.7 months (95% CI, 8.5-not estimable). There was a 12-month overall survival rate of 54.3% (95% CI, 37.9-68.1). Confirmed overall response rate was 18.2% (95% CI, 8.2-32.7). Median duration of response was not reached. A total of 37 participants were able to be evaluated for PD-L1 expression and 7 of 8 responding participants had PD-L1-positive tumors.

The 2018 National Comprehensive Cancer Network® Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for bladder cancer gives a 2A recommendation for avelumab for locally or advanced metastatic disease for urothelial carcinoma.

Key Words:

Bavencio®, avelumab, Merkel cell carcinoma, urothelial carcinoma, bladder cancer, skin cancer

Approved by Governing Bodies:

On March 23, 2017, avelumab achieved accelerated approval status by the FDA for the treatment of metastatic Merkel cell carcinoma for individuals age 12 years and older. This approval was based on tumor response and duration of response. Continued approval for this indication may be subject to verification and description of clinical benefit in confirmatory trials which are underway.

On May 9, 2017, the Food and Drug Administration granted accelerated approval to avelumab for patients with locally advanced or metastatic urothelial carcinoma whose disease progressed during or following platinum platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum containing chemotherapy.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

CPT Codes:

As of 01/01/2018, there is a specific code for avelumab:

J9023 Injection, avelumab, 10 mg **(Effective 01/01/2018)**

Previous Coding:

Prior to 01/01/2018, there was no specific code for avelumab:

J9999 Not otherwise classified, antineoplastic drugs [when specified as avelumab]

References:

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7. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology®. Urothelial Carcinoma (V.5.2017). Revised May 25, 2017.Available at: www.nccn.org/index.asp.
8. Nghiem P, Kaufman HL, Bharmal M, et al. Systematic literature review of efficacy, safety and tolerability outcomes of chemotherapy regimens in patients with metastatic Merkel cell carcinoma. Future Oncol. 2017 Mar 28.
9. U.S. Food and Drug Administration. Drug Approvals and Databases. FDA grants accelerated approval to avelumab for urothelial carcinoma. Available at: www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm557162.htm.

Policy History:

Adopted for Blue Advantage, June, 2017
Available for comment June 16, 2017 to July 31, 2017
Medical Policy Group, December 2017
Medical Policy Group, October 2018 (**2**): Updates to Key Words – added bladder cancer and skin cancer; Policy section with clarification - added when used as a single agent to urothelial carcinoma criteria; no change to intent.
Medical Policy Group, November 2018