DRAFT

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:
Imfinzi (durvalumab)

Policy #: 673
Category: Pharmacy

Effective Date: December 2, 2018
Last 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:

Imfinzi (durvalumab) is a human monoclonal programmed death ligand 1 (PD-L1) blocking antibody. Durvalumab works by blocking the interaction of programmed cell death ligand 1 (PD-L1) with the PD-1 and CD80 (B7.1) molecules. 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.

Some tumors express the PD-L1 protein which allows tumors to evade detection by the immune system. PD-L1 is also expressed by immune cells. PD-1 is a key receptor; when bound to PD-L1 it suppresses T-cell mediated immune responses. For those tumors which express PD-L1, blocking this pathway allows T-cells to recognize and kill tumor cells. PD-L1 expression can be measured in either the tumor cells or the immune cells. Currently, the assays for PD-L1 expression are not standardized.

Policy:

Effective for dates of service on or after December 2, 2018

Blue Advantage will treat **imfinzi (durvalumab)** 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. Inoperable or metastatic transitional-cell urothelial carcinoma histologically or cytologically confirmed; **and**
B. One of the following:
    1. Disease has progressed during or following platinum-containing therapy; **or**
    2. Disease has progressed within 12 months of neoadjuvant or adjuvant treatment with platinum-containing therapy; **and**
C. Current Eastern Cooperative Oncology Group (ECOG) performance status of 0-1; **and**
D. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **and**
E. Does not have *any* of the following:
    1. History of immunodeficiency; **or**
    2. History of severe autoimmune disease; **or**
    3. Require systemic immunosuppression; **or**
    4. Active immune-mediated disease; **or**
    5. Severe or life-threatening infection; **or**
    6. Untreated central nervous system (CNS) metastases.

Blue Advantage will treat **imfinzi (durvalumab)** as a **covered benefit** when used as **consolidation therapy** for the treatment of **unresectable stage III non-small cell lung cancer** when all of the following criteria are met:

A. Stage III locally advanced, unresectable non-small cell lung cancer histologically or cytologically confirmed; **and**
B. Disease has **not** progressed after definitive chemoradiation; **and**
C. Individual has a current Eastern Cooperative Oncology Group (ECOG) performance status of 0-1; **and**

D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **and**
E. Until disease progression or a maximum of 12 months of treatment; **and**
F. Individual does not have *any* of the following:
    1. History of immunodeficiency; **or**
    2. History of severe autoimmune disease; **or**
    3. Require systemic immunosuppression; **or**
    4. Active immune-mediated disease; **or**
    5. Severe or life-threatening infection; **or**
    6. Untreated central nervous system (CNS) metastases.

Effective for dates of service on and after August 8, 2017 and prior to December 2, 2018:
Blue Advantage will treat **imfinzi (durvalumab)** 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:

F. Inoperable or metastatic transitional-cell urothelial carcinoma histologically or cytologically confirmed; **and**
G. One of the following:
    1. Disease has progressed during or following platinum-containing therapy; **or**
    2. Disease has progressed within 12 months of neoadjuvant or adjuvant treatment with platinum-containing therapy; **and**
H. Current Eastern Cooperative Oncology Group (ECOG) performance status of 0-1; **and**
I. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **and**
J. Does not have *any* of the following:
    1. History of immunodeficiency; **or**
    2. History of severe autoimmune disease; **or**
    3. Require systemic immunosuppression; **or**
    4. Active immune-mediated disease; **or**
    5. Severe or life-threatening infection; **or**
    6. Untreated central nervous system (CNS) metastases.

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:

Urothelial bladder cancers arise from the epithelium of the bladder and are the sixth most common form of cancer in the US. It is estimated that in 2018, approximately 81,190 Americans will be diagnosed with bladder cancer, and an estimated 17,240 will die from this disease.

In an open-label, phase 1/2 study by Massard and colleagues, the safety and efficacy of durvalumab was investigated. A total of 61 participants with inoperable or metastatic solid tumors were treated with durvalumab every 2 weeks for up to 12 months. The majority of participants (93.4%) had received one or more prior systemic therapies and 31.1% had received three or more prior systemic therapies. The primary endpoint was safety and the secondary endpoint was objective response rate. Median duration of follow-up was 4.3 months. A total of 63.9% (39/61) individuals reported a treatment related adverse event (AE). The most common AEs were low grade and included fatigue, diarrhea, and decreased appetite. There were 3 participants who experienced grade 3 AEs and there were no reported grade 4 or 5 events. In 42 participants, the objective response rate was 31.0% (95% confidence interval [CI], 17.6 to 47.1) and 46.4% (95% CI, 27.5 to 66.1) in the PD-L1-positive subgroup, and 0% (95% CI, 0.0 to 23.2) in the PD-L1-negative subgroup.

Powles and associates (2017) reported the interim results of the 2016 Massard study. A total of 191 subjects received treatment until confirmed progressive disease or for up to 12 months. The results were compared with historical controls. At this update, the primary outcome of ORR was 17.8% or 34 of 191 (95% CI: 12.7%-24.0%), which is lower than the previously reported 31%. Secondary outcomes included progression-free survival and overall survival, which were reported as 1.5 months (95% CI, 1.4-1.9 months) and 18.2 months (95% CI, 8.1 months to not estimable), respectively. Seven complete responses were reported. AEs of any grade were reported in 60.7% (116/191) of participants, with 6.8% (13/191) of the AEs being a grade 3 or 4. There were 2 treatment-related AEs which resulted in death. More results are expected as the study is ongoing.

The National Comprehensive Cancer Network (NCCN) Bladder Cancer Guidelines (V5.2018) has a 2A recommendation for the use of durvalumab as an alternative preferred treatment regimen for individuals with locally advanced or metastatic bladder cancer.

Non-Small Cell Lung Cancer (NSCLC)

Lung cancer is the second most common type of cancer. NSCLC accounts for 80-85% of all lung cancers. The ACS estimates that in 2018 approximately 234,030 new cases of lung cancer will be diagnosed and 154,050 deaths related to lung cancer will occur. The ACS notes that lung cancer is the leading cause of cancer death, killing more people than colon, breast and prostate cancers combined

Antonia and associates (2017) reported on an interim analysis of a randomized, double-blind, phase 3 study which compared durvalumab to placebo as a consolidation therapy in individuals with stage III, locally advanced, unresectable NSCLC who had not progressed after platinum-based chemoradiotherapy. After chemoradiation individuals were randomized to receive either durvalumab or a placebo. Individuals receiving durvalumab could continue the drug until disease progression. The coprimary end points were identified as progression-free survival (as defined

by the Response Evaluation Criteria in Solid Tumors [RECIST] and overall survival. A total of 709 individuals were included in the study. Median progression-free survival was16.8 months in the durvalumab group (95% confidence interval [CI], 13.0 to 18.1) compared to 5.6 months in the placebo group (95% CI, 4.6 to 7.8) (stratified hazard ratio for disease progression or death, 0.52; 95% CI, 0.42 to 0.65; two-sided $p<0.001$). The 12 and 18 month progression-free survival rate in the durvalumab group was 55.9% and 44.2% respectively compared to the placebo group rates of 35.3% and 27.0% respectively. Grade three or four adverse events (AEs) were reported in 29.9% of the durvalumab group and 26.1% of the placebo group, with pneumonia noted as the most common AE in both groups. AEs leading to death occurred in both the durvalumab and placebo groups, at 4.4% and 5.6% respectively. The longer progression-free survival was documented across all subgroups of individuals, including level of PD-L1 positive tumor cells. The authors noted that the difference in progression-free survival was also present in those in whom a response was not expected.

The National Comprehensive Cancer Network (NCCN) Non-Small Cell Lung Cancer Guidelines (V6. 2018) includes durvalumab as a category 2A treatment option following definitive chemoradiation. Durvalumab therapy is recommended for up to 12 months.

Key Words:

Imfinzi, durvalumab, urothelial carcinoma, bladder cancer, non-small cell lung cancer , NSCLC

Approved by Governing Bodies:

On May 1, 2017, the U.S. Food and Drug Administration (FDA) approved durvalumab for the treatment of individuals with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. This indication was approved under an accelerated process and is based on tumor response rate and duration of response. The FDA also included a contingency that continued approval may be based upon verification and description of clinical benefit in confirmatory trials.

On February 16, 2018, the FDA approved durvalumab for patients with unresectable stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.

Benefit Application:

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

ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:	**J9999**	Not otherwise classified, antineoplastic drugs [when specified as durvalumab]

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Policy History:

Adopted for Blue Advantage, June 2017
Available for comment June 23, 2017 through August 7, 2017
Medical Policy Group, May 2018
Medical Policy Group, October 2018 (2): Updates to Description, Key Points, Approved by Governing Bodies, and References; Added Key Words – non-small cell lung cancer and NSCLC; updated Policy section to include coverage criteria for non-small cell lung cancer.
Available for comment October 18, 2018 through December 2, 2018.
