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:
Tecentriq™ (Atezolizumab)

Policy #: 668
Category: Pharmacology
Effective Date: December 1, 2017
Latest Review Date: September 2017

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:

Atezolizumab is an anti- programmed death ligand 1 monoclonal antibody (PD-L1). It blocks the interactions with both PD-1 and B7.1 receptors. This releases the PD-L1/PD-1 mediated inhibition of the immune response, including activation of the anti-tumor immune response without inducing antibody dependent cellular cytotoxicity. 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 or after December 1, 2017 and prior to November 1, 2018:
Blue Advantage will treat **Tecentriq™ (atezolizumab)** as a **covered benefit** for **first-line treatment of locally advanced or metastatic urothelial carcinoma** when the following criteria are met:

- Individual is ineligible for cisplatin treatment, defines as having one or more of the following risk factors for cisplatin toxicity:
    - ECOG performance status of 0-2;
    - Glomerular filtration rate less than 60mL/min;
    - Hearing loss (measured at audiometry) of 25 dB at two contiguous frequency
    - Grade 2 or greater peripheral neuropathy

Blue Advantage will treat **Tecentriq™ (atezolizumab)** as a **covered benefit** when **ALL** of the following are met:

- Has not received treatment with another PD-1 or PD-L1 agent (e.g., nivolumab or pembrolizumab); **AND**
- Current Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; **AND**
- Individual does not have an active autoimmune disease or chronic condition requiring systemic immunosuppression; **AND**
- **Follows individual criteria for specific oncologic indication as listed BELOW:**

Blue Advantage will treat **Tecentriq™ (atezolizumab)** as a **covered benefit** for the treatment of **locally advanced or metastatic urothelial carcinoma** when the following criteria are met:

- Disease has progressed during or following platinum-containing chemotherapy (for example, cisplatin); **OR**
- Disease has progressed within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Blue Advantage will treat **Tecentriq™ (atezolizumab)** as a **covered benefit** for the treatment of **metastatic non-small cell lung cancer** when the following criteria are met:

- Disease has progressed during or following platinum-containing chemotherapy (for example, cisplatin); **AND**

- When EGFR or ALK genomic tumor aberrations are present, should have disease progression on FDA-approved therapy for those aberrations prior to receiving Tecentriq™.

Blue Advantage will treat **Tecentriq™ (atezolizumab)** as a **non-covered benefit** and as investigational when the above criteria are not met.

Effective for dates of service December 1, 2016 through November 30, 2017:
Blue Advantage will treat **Tecentriq™ (atezolizumab**) as a **covered benefit** for the treatment of **locally advanced or metastatic urothelial carcinoma** when the following criteria are met:

- Disease has progressed during or following platinum-containing chemotherapy (for example, cisplatin); **OR**
- Disease has progressed within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; **AND**
- Individual has a current Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; **AND**
- Individual has not received treatment with a PD-1 agent (for example, nivolumab or pembrolizumab); **AND**
- Individual does not have an active autoimmune disease.

Blue Advantage will treat **Tecentriq™ (atezolizumab**) as a **covered benefit** for the treatment of **metastatic non-small cell lung cancer** when the following criteria are met:

- Disease has progressed during or following platinum-containing chemotherapy (for example, cisplatin); **OR**
- When EGFR or ALK genomic tumor aberrations are present, should have disease progression on FDA-approved therapy for those aberrations prior to receiving Tecentriq™.

Blue Advantage will treat **Tecentriq™ (atezolizumab)** as a **non-covered benefit** and as **investigational** when the above criteria are not met.

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 Carcinoma

Urothelial carcinoma is the most common type of bladder cancer and occurs in the urinary tract system, involving the bladder and related organs. The American Cancer Society estimates that in 2017 there will be approximately 79,030 new cases of bladder cancer (about 60,490 in men and 18,540 in women) and 16,870 deaths from bladder cancer (about 12,240 in men and 4,630 in women) in the United States.

On May 18, 2016, the FDA approved atezolizumab for the treatment of individuals with locally advanced or metastatic urothelial cancer who had disease progression during or following platinum-containing chemotherapy or whose disease progressed within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. This indication was approved under an accelerated process based on tumor response rate and durability of response. The FDA stated that continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

A 2014 phase I study provided the initial evidence of the safety and efficacy of atezolizumab for the treatment of metastatic bladder cancer. Results of the phase I study were expanded into a multicenter, single-arm, phase II trial of individuals at least 18 years of age with inoperable locally advanced or metastatic urothelial carcinoma whose disease had progressed after previous platinum-based chemotherapy. Key inclusion criteria were ECOG performance status of 0 or 1, measurable disease defined by Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1), adequate hematological and end-organ function, and no autoimmune disease, active infections or corticosteroid use. Treatment consisted of intravenous atezolizumab (1200 mg every 3 weeks). The primary endpoint of the study was objective response rate based on both the independent review facility-assessed objective response rate and the investigator-assessed objective response rate. Between May 13, 2014, and Nov 19, 2014, 315 individuals from 70 major academic medical centers and community oncology practices in Europe and North America were enrolled into the study. Of the 315, a total of 310 received atezolizumab (5 enrollees later did not meet eligibility criteria and were not dosed with study drug). The primary analysis showed that compared with a historical control overall response rate of 10%, treatment with atezolizumab resulted in a significantly improved RECIST v1.1 objective response rate for each prespecified immune cell group (IC2/3: 27% [95% confidence interval (CI), 19-37], $p<0.0001$; IC1/2/3: 18% [13-24], $p=0.0004$) and in all subjects (15% [11-20], $p=0.0058$). Of note, the objective response rate was 8% in subjects who were classified as "negative" for PD-L1 expression-lower than historical control objective response rate. At longer follow-up of all 310 subjects, objective response rates were 26% (95% CI, 18-36) in the IC2/3 group, 18% (13-24) in the IC1/2/3 group, and 15% (11-19) overall in all 310 subjects. At a median follow-up of 11.7 months (95% CI, 11.4-12.2), ongoing responses were recorded in 38 (84%) of 45 subjects. The Cancer Genome Atlas (TCGA) subtypes and mutation load were found to be independently predictive for response to atezolizumab. Grade 3-4 treatment-related adverse events, of which fatigue was the most common (5 individuals [2%]), were low and occurred in 50 (16%) of 310 treated subjects. There were no cases of febrile neutropenia. A total of 15 (5%) of 310 treated subjects had grade 3-4 immune-mediated adverse events, with pneumonitis, increased aspartate aminotransferase, increased alanine aminotransferase, rash, and dyspnea being the most

common. There were no treatment-related deaths during the study. The authors concluded that atezolizumab showed durable activity and good tolerability in this particular population.

A single-arm, multi-center phase II trial studied the safety and efficacy of atezolizumab as first-line chemotherapy for cisplatin-ineligible, locally advanced or metastatic urothelial carcinoma. A total of 47 academic medical centers and community oncology practices in seven countries participated. Cohort 1 consisted of subjects without previous treatment for metastatic urothelial cancer. Eligibility criteria included: inoperable, locally advanced or metastatic urothelial cancer (renal pelvis, ureters, bladder or urethra), measurable disease per RECIST, a tumor sample available for PD-L1 testing, and an ECOG performance status of 2 or less. Cisplatin ineligibility was defined as having one or more of the following: glomerular filtration rate (GFR) more than 30 mL/min and less than 60 mL/min (Cockcroft-Gault formula), a hearing loss measured by audiometry of 25 dB at two contiguous frequencies, grade 2 or greater peripheral neuropathy (that is, sensory alteration or paresthesias including tingling), or an ECOG performance score of 2. Cohort II was described earlier by Rosenberg and colleagues and had enrolled subjects previously treated with platinum-based chemotherapy. A total of 123 subjects were enrolled between June 9, 2014 and March 30, 2015. Of those, 119 were treated with at least one dose of intravenous atezolizumab every 21 days until unacceptable toxicity or investigator-assessed radiographic progression. At 17.2 months median follow-up, the objective response rate was 23% (95% CI, 16 to 31), the complete response rate was 9% (n=11), and 19 of 27 responses were ongoing. Median response duration was not reached. Responses occurred across all PD-L1 and poor prognostic factor subgroups. Median progression-free survival (PFS) was 2.7 months (2.1 to 4.2). Median overall survival (OS) was 15.9 months (10.4 to not estimable). Tumor mutation load was associated with response. A total of 114 (96%) of subjects had an adverse event and 79 (66%) had a treatment-related event. Treatment-related adverse events that occurred in at least 10% of subjects were fatigue, diarrhea and pruritus. One treatment-related death due to sepsis was reported. Adverse events leading to discontinuation of treatment occurred in 9 subjects and immune-mediated events occurred in 14 (12%) subjects. The authors concluded "overall, atezolizumab showed promising response durability and survival, coupled with a low incidence of clinically relevant toxicities despite numerous comorbidities in this population."

The National Comprehensive Cancer Network (NCCN) Bladder Cancer Guidelines (V5. 2017) and 2017 NCCN Drug Compendia currently indicate that atezolizumab may be used as a second line or systemic therapy for locally advanced or metastatic disease (2A designation) under specific conditions.

Non-Small Cell Lung Cancer

Lung cancer is the leading cause of death in the United States, with only 17.7% of patients surviving five or more years after diagnosis. The primary risk factor for lung cancer is smoking tobacco. Non-small cell lung cancer (NSCLC) accounts for more than 85% of all lung cancer cases. The two major types of NSCLC are non-squamous carcinoma and squamous cell (epidermoid) carcinoma.

Treatment approaches for NSCLC include surgery, radiation therapy (RT), and chemotherapy. For patients with stage I or II disease, surgery is the recommended option with the best chance for cure. RT can play a role in all stages of NSCLC as either definitive or palliative therapy.

Adjuvant chemotherapy has been shown to improve survival in patients with early-stage disease and completely resected NSCLC.

On October 18, 2016, FDA approved atezolizumab for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose disease progressed during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab. Similar drugs for this indication are Opdivo and Keytruda. The FDA's approval was based on positive results of the randomized phase III OAK and phase II POPLAR studies. The OAK trial investigated the safety and effectiveness of atezolizumab as compared to docetaxel in 1225 individuals. The primary analysis population consisted of the first 850 randomized subjects. Median overall survival for the atezolizumab group (n=425) was 13.8 months compared to 9.6 months for those treated with docetaxel (n=425). At the time of this writing, the OAK trial is not available in the published literature.

The POPLAR trial (open-label, multicenter, randomized study to investigate the efficacy and safety of atezolizumab compared with docetaxel in patients with non-small cell lung cancer after platinum failure) by Fehrenbacher and colleagues. This phase II trial consisted of individuals with NSCLC who progressed on post-platinum chemotherapy that were recruited from 61 academic medical centers and community oncology practices in 13 countries in Europe and North America. Key inclusion criteria were ECOG performance status 0 or 1, measurable disease by RECIST v1.1, and adequate hematological and end-organ function. Key exclusion criteria were autoimmune or chronic viral diseases, active or untreated CNS metastases, history of pneumonitis, or previous treatment with docetaxel, CD137 agonists, anti-CTLA4, anti-PD-L1, or anti-PD-L1 therapeutic antibodies, or PD-L1-PD1 pathway-targeting agents. Individuals were stratified by PD-L1 tumor-infiltrating immune cell status, histology, and previous lines of therapy, and randomly assigned (1:1) to receive intravenous atezolizumab 1200 mg or docetaxel 75 mg/m^2 once every 3 weeks. The primary endpoint was OS in the intention-to-treat population and PD-L1 subgroups at 173 deaths. Between Aug 5, 2013 and March 31, 2014, a total of 144 subjects were randomized to the atezolizumab group, and 143 to the docetaxel group. Of these, 142 individuals received at least one dose of atezolizumab and 135 received docetaxel. OS in the intention-to-treat population was 12.6 months (95% CI, 9.7-16.4) for atezolizumab versus 9.7 months (8.6-12.0) for docetaxel (hazard ratio [HR] 0.73 [95% CI, 0.53-0.99]; p=0.04). OS in individuals without PD-L1 expression in either tumor cells or tumor-infiltrating immune cells in the atezolizumab group was similar to that in the docetaxel group. An increase in OS was associated with increasing PD-L1 expression. In the exploratory analysis, individuals with pre-existing immunity had improved OS with atezolizumab. A total of 11 (8%) subjects in the atezolizumab group discontinued because of adverse events versus 30 (22%) subjects in the docetaxel group. Additionally, 16 (11%) subjects in the atezolizumab group versus 52 (39%) subjects in the docetaxel group had treatment-related grade 3-4 adverse events, and 1 (< 1%) subject in the atezolizumab group versus 3 (2%) subjects in the docetaxel group died from a treatment-related adverse event. The authors concluded that atezolizumab significantly improved survival compared with docetaxel in individuals with previously treated NSCLC. Improvement correlated with PD-L1 immunohistochemistry expression on tumor cells and tumor-infiltrating immune cells, suggesting that PD-L1 expression is predictive for atezolizumab benefit.

The NCCN NSCLC guidelines (V5.2017) and the 2017 NCCN Drug Compendium both indicate that atezolizumab may be used for the treatment of NSCLC following progression of metastatic disease (2A designation) under specific conditions.

Key Words:

Tecentriq, Atezolizumab, Urothelial Carcinoma, Non-Small Cell Lung Cancer (NSCLC)

Approved by Governing Bodies:

On May 18, 2016, the U.S. FDA gave accelerated approval to the atezolizumab injection (Tecentriq, Genentech, Inc) for the treatment of patients with locally advanced or metastatic urothelial carcinoma 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. Atezolizumab is a programmed death-ligand 1 (PD-L1) blocking antibody.

On October 18, 2016, FDA approved atezolizumab (Tencentriq, Genentech Oncology) for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose disease progressed during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab.

Benefit Application:

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

Current Coding:

CPT Codes:

J9022 Injection, atezolizumab, 10mg **(Effective 01/01/2018)**

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

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

References:

1. Alsina M, Moehler M, Hierro C, et al. Immunotherapy for gastric cancer: a focus on immune checkpoints. Target Oncol. 2016 Aug; 11(4):469-77.
2. American Cancer Society. Bladder Cancer. Available at: www.cancer.org/cancer/bladdercancer/detailedguide/index.
3. American Cancer Society. Lung Cancer - Non-Small Cell. Available at: www.cancer.org/Cancer/LungCancer-Non-SmallCell/DetailedGuide/index.

4. Atezolizumab. In: DrugPoints System [Electronic Version]. Truven Health Analytics. Greenwood Village, Colo. Last updated May 20, 2016. Available at: www.micromedexsolutions.com.
5. Balar AV, Galsky MD, Rosenberg JE, et al; IMvigor210 Study Group. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017; 389(10064):67-76.
6. Fehrenbacher L, Spira A, Ballinger M, et al; POPLAR study group. atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomized controlled trial. Lancet. 2016 Apr 30: Volume 387, No. 10030, 1837–1846.
7. García-Teijido P, Cabal ML, Fernández IP, Pérez YF. Tumor-infiltrating lymphocytes in triple negative breast cancer: the future of immune targeting. Clin Med Insights Oncol. 2016; 10 (Suppl 1):31-39.
8. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014; 515(7528):563-567.
9. Hoffmann-La Roche. A randomized phase 3 study of atezolizumab (an engineered anti-PDL1 antibody) compared to docetaxel in patients with locally advanced or metastatic non-small cell lung cancer who have failed platinum therapy - "OAK". NLM Identifier: NCT02008227. Last updated on November 1, 2016. Available at: clinicaltrials.gov/ct2/show/record/NCT02008227.
10. Mahoney KM, Freeman GJ, McDermott DF. The Next immune-checkpoint inhibitors: PD-1/PD-L1 blockade in melanoma. Clin Ther. 2015; 37(4):764-782.
11. McDermott DF, Sosman JA, Sznol M, et al. Atezolizumab, an anti-programmed death-ligand 1 antibody, in metastatic renal cell carcinoma: long-term safety, clinical activity, and immune correlates from a phase Ia study. J Clin Oncol. 2016; 34(8):833-842.
12. National Comprehensive Cancer Network®. NCCN Drugs & Biologic Compendium™ Available at: www.nccn.org.
13. NCCN Clinical Practice Guidelines in Oncology™. © 2016 National Comprehensive Cancer Network, Inc. Bladder Cancer. V5.2017. Revised May 25, 2017. Available at: www.nccn.org/index.asp.
14. NCCN Clinical Practice Guidelines in Oncology™. © 2016 National Comprehensive Cancer Network, Inc. Bladder Cancer. V9.2017. Revised September 28, 2017. Available at: www.nccn.org/index.asp.
15. Powles T, Eder JP, Fine GD, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature. 2014; 515(7528):558-562.
16. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016 Mar 4. Volume 387, No. 10031, p1909–1920.
17. Tecentriq™ [Product Information]. South San Francisco, CA. Genentech, Inc. May 2016. Available at: www.gene.com/download/pdf/tecentriq_prescribing.pdf U.S. Food and Drug Administration Premarket Approval (PMA) Database. Ventana PD-L1(SP142) CDX Assay. Rockville, MD: FDA. May 18, 2016. Available at: www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160002.

18. U.S. Food & Drug Administration (FDA). Approved Drugs. Atezolizumab (TECENTRIQ). 10/19/2016. Available at: www.fda.gov/Drugs/InformationOnDrugs/Approved Drugs/ucm525780.htm

Policy History:

Adopted for Blue Advantage, September 2016
Available for comment September 29, 2016 to December 1, 2016
Medical Policy Group, October 2016
Medical Policy Group, November 2016
Medical Policy Group, October 2017
Available for comment October 3, 2017 to November 30, 2017
Medical Policy Group, December 2017
Medical Policy Group, November 2018