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:
Keytruda (pembrolizumab)

Policy #: 666
Category: Pharmacology
Effective Date: January 27, 2018
Latest Review Date: November 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:

Keytruda® (pembrolizumab) is a humanized monoclonal antibody that works by increasing the ability of the body's immune system to help detect and fight tumor cells. Keytruda is a PD-1 inhibitor that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. When these proteins are blocked, the "brakes" on the immune system are released increasing its ability to destroy cancer cells.

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 January 27, 2018, and prior to November 1, 2018:

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** when **ALL** of the following are met:

- Has not received treatment with another PD-1 agent (e.g., nivolumab); **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 **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **unresectable or metastatic melanoma**, excluding primary ocular melanoma when being used as a **single agent** for **ONE** of the following indications:

- Used as first-line therapy in untreated disease; **OR**
- Used as second-line or subsequent therapy for documented disease progression while receiving or since completing most recent therapy; **OR**
- Used after maximum clinical benefit from BRAF targeted therapy; **OR**
- Used as re-induction therapy for progression/relapse greater than 3 months after treatment discontinuation.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **metastatic non-small cell lung cancer** when used as a **single agent as first line therapy** when the treatment meets **ALL** of the following:

- Cytologically confirmed stage IV NSCLC; **AND**
- Tumor expresses PD-L1 gene on at least 50% of tumor cells; **AND**
- No EGFR, ALK, ROS1, or BRAF genomic tumor aberrations are present.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **metastatic non-small cell lung cancer** when used as a **single agent for second or subsequent line of therapy** when the treatment meets **ALL** of the following criteria:

- Tumor expresses PD-L1 gene expression level greater than or equal to 1% with demonstrated disease progression on or after platinum-containing chemotherapy; **AND**

- When ALK or EGFR genomic tumor aberrations are present, must have disease progression on U.S. Food and Drug Administration approved therapy for the aberrations prior to receiving pembrolizumab.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for **first line treatment of metastatic nonsquamous non-small cell lung cancer** when the treatment meets **ALL** of the following:

- Used in combination with carboplatin and pemetrexed; **AND**
- Cytologically confirmed stage IIIb or IV NSCLC; **AND**
- Tumors are EGFR, ALK, ROS1, or BRAF negative or unknown, and PD-L1 less than 50%.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **recurrent or metastatic head and neck squamous cell carcinoma** (HNSCC) **(** non-nasopharyngeal cancer) when used as a **single agent** for disease progression on or after platinum-based chemotherapy.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **relapsed or refractory classical Hodgkin lymphoma** when being used as a **single agent** when treatment meets the following:

- Used as additional therapy for refractory disease if Deauville 4-5; **OR**
- Used as additional therapy for relapsed disease following treatment with brentuximab vedotin.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **colorectal cancer (defective mismatch repair/high microsatellite instability [dMMR/MSIH] only)** when used as a **single agent** for **ONE** of the following indications:

- Primary treatment of unresectable metachronous metastases following previous adjuvant FOLFOX or CapeOX in past 12 months; **OR**
- Initial therapy for unresectable advanced or metastatic disease who are not appropriate for intensive therapy; **OR**
- Subsequent therapy for unresectable advanced or metastatic disease following previous oxaliplatin- irinotecan- and/or fluoropyrimidine-based therapy (if nivolumab or pembrolizumab was not previously given).

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **Merkel-cell carcinoma** when used as a **single agent** for the treatment of distant metastatic disease or disseminated recurrence with or without surgery or radiation therapy.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **unresectable or metastatic solid tumors (dMMR/MSIH only)** as a **single agent** for disease progression following prior treatment with no other satisfactory alternative treatment option.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **locally advanced or metastatic urothelial carcinoma** (**includes cancer of urethra, upper**

genitourinary tract, and prostate) when used as a **single agent** for **ONE** of the following indications:

- Has disease progression on or after platinum-containing chemotherapy; **OR**
- Has disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; **OR**
- First-line therapy in cisplatin ineligible patients.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma** when used as a **single agent** and **ALL** of the following are met:

- Tumor expresses PD-L1 level greater than or equal to 1; **AND**
- Has disease progression on or after two or more prior lines of therapy including fluoropyrimidine – and platinum-containing chemotherapy; **AND**
- When HER2 tumor aberrations are present, must have disease progression on HER2 targeted therapy prior to receiving pembrolizumab.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **non-covered benefit** and as **investigational** when the above criteria are not met.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **non-covered benefit** and as **investigational** for disease progression following prior anti-PD-1 therapy (e.g., nivolumab (Opdivo), atezolizumab (Tecentriq), avelumab (Bavencio), and durvalumab (Imfinzi)).

Effective for dates of service on or after July 1, 2017 through January 26, 2018:

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** when **ALL** of the following are met:

- Has not received treatment with another PD-1 agent (e.g., nivolumab); **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 **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **unresectable or metastatic melanoma**, excluding primary ocular melanoma when being used as a **single agent** for **ONE** of the following indications:

- Used as first-line therapy in untreated disease; **OR**
- Used as second-line or subsequent therapy for documented disease progression while receiving or since completing most recent therapy; **OR**
- Used after maximum clinical benefit from BRAF targeted therapy; **OR**
- Used as re-induction therapy for progression/relapse greater than 3 months after treatment discontinuation.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **metastatic non-small cell lung cancer** when used as a **single agent as first line therapy** when the treatment meets **ALL** of the following:

- Cytologically confirmed stage IV NSCLC; **AND**
- Tumor expresses PD-L1 gene on at least 50% of tumor cells; **AND**
- No sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocations.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **metastatic non-small cell lung cancer** when used as a **single agent for second or subsequent line of therapy** when the treatment meets **ALL** of the following criteria:

- Tumor expresses PD-L1 gene expression level greater than or equal to 1% with demonstrated disease progression on or after platinum-containing chemotherapy; **AND**
- When ALK or EGFR genomic tumor aberrations are present, must have disease progression on U.S. Food and Drug Administration approved therapy for the aberrations prior to receiving pembrolizumab.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **recurrent or metastatic head and neck squamous cell carcinoma** (HNSCC) **(** non-nasopharyngeal cancer) when used as a **single agent** for disease progression on or after platinum-based chemotherapy.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **relapsed or refractory classical Hodgkin lymphoma** when being used as a **single agent** when treatment meets the following:

- Used as additional therapy for refractory disease if Deauville 4-5; **OR**
- Used as additional therapy for relapsed disease following treatment with brentuximab vedotin.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **colorectal cancer** when used as a **single agent** for **ONE** of the following indications:

- Primary treatment of unresectable metachronous metastases following previous adjuvant FOLFOX or CapeOX in past 12 months; **OR**
- Initial therapy for unresectable advanced or metastatic disease who are not appropriate for intensive therapy; **OR**
- Subsequent therapy for unresectable advanced or metastatic disease following previous oxaliplatin- irinotecan- and/or fluoropyrimidine-based therapy (if nivolumab or pembrolizumab was not previously given).
  **Note: for defective mismatch repair/high microsatellite instability (dMMR/MSI-H) only*

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **Merkel-cell carcinoma** when used as a **single agent** for the treatment of distant metastatic disease or disseminated recurrence with or without surgery or radiation therapy.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **non-covered benefit** and as **investigational** when the above criteria are not met.

Effective for dates of service on or after November 6, 2016 and prior to July 1, 2017:
Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **unresectable or metastatic melanoma**, excluding primary ocular melanoma when being used as a **single agent** and the treatment meets **ALL** the following criteria:

- Will be used as first-line therapy in untreated disease; **OR**
- Will be used as second-line or subsequent therapy for documented disease progression while receiving or since completing most recent therapy; **AND**
- Current Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; **AND**
- Has not received treatment with another PD-1 agent (e.g., nivolumab); **AND**
- Individual does not have an active autoimmune disease.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **metastatic non-small cell lung cancer** when used as a **single agent** and treatment meets **ALL** of the following criteria:

- Tumor expresses PD-L1 gene with demonstrated disease progression on or after platinum-containing chemotherapy; **AND**
- When ALK or EGFR genomic tumor aberrations are present, must have disease progression on U.S. Food and Drug Administration approved therapy for the aberrations prior to receiving pembrolizumab; **AND**
- Current Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; **AND**
- Has not received treatment with another PD-1 agent (e.g., nivolumab); **AND**
- Individual does not have an active autoimmune disease.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **recurrent or metastatic head and neck squamous cell carcinoma** (HNSCC) with disease progression on or after platinum-based chemotherapy.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **relapsed or refractory classical Hodgkin lymphoma** when being used as a **single agent**.

Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **non-covered benefit** and as **investigational** when the above criteria are not met.

Effective for dates of service September 1, 2015 through November 5, 2016:
Blue Advantage will treat **Keytruda® (pembrolizumab)** as a **covered benefit** for the treatment of **unresectable or metastatic melanoma**, excluding primary ocular melanoma when being used as a **single agent** and the individual does not have an active autoimmune disease.

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:

Metastatic Melanoma (MM)

Metastatic melanoma is an aggressive disease. The median survival for individuals with stage IV melanoma is 6–10 months, and less than 5% of individuals survive beyond 5 years. It has been estimated that approximately 50% of cutaneous melanomas carry the mutated BRAF gene which keeps the protein production constantly activated and driving cell growth. Mutations of the BRAF gene have been associated with shorter progression-free intervals and overall decreased survival. Most of these mutations occur at the amino acid position 600, the most common of which results in the V600E amino acid substitution. When discovered early, melanoma can usually be cured with surgery. Once metastasis occurs, the prognosis is usually poor. Treatment of metastatic melanoma may include lymphadenectomy, immunotherapy, radiation therapy, chemotherapy or participation in a clinical trial. Despite recent advances with melanoma treatment, there remains a challenge since there are few effective treatment options for individuals who relapse or do not respond to ipilimumab or BRAF inhibitors.

The National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines in Oncology on Melanoma (2017) address the challenges with treatment for stage IV melanoma:

> The therapeutic landscape for metastatic melanoma is rapidly changing with the recent development of novel agents, which has demonstrated better efficacy than traditional chemotherapy. The first generation of novel targeted and immunotherapy agents (i.e., vemurafenib, dabrafenib, ipilimumab) demonstrated significantly improved response rates and outcomes compared with conventional therapies. Subsequently, a number of ongoing or recently completed phase II and phase III trials testing new immunotherapies, targeted therapies, and combination regimens have yielded noteworthy results. A second generation of effective agents and combination regimens are now available for treatment of advanced unresectable or metastatic melanoma.

On September 4, 2014, pembrolizumab achieved accelerated approval and breakthrough therapy status by the FDA, because it provided an option for individuals with late-stage cancer who have been through several other therapies and yet still have disease progression. The FDA approved pembrolizumab (as a single agent) for the treatment of unresectable or metastatic melanoma and disease progression in individuals following ipilimumab, if BRAF V600 mutation positive, a BRAF inhibitor. BRAF inhibitors are dabrafenib (Tafinlar® oral) or vemurafenib (Zelboraf® oral). On December 18, 2015, the FDA expanded the label for pembrolizumab in the treatment of unresectable or metastatic melanoma. The expanded use now includes the initial treatment of individuals with unresectable or metastatic melanoma.

The FDA accelerated approval of pembrolizumab was based on an open-label, multicenter expansion cohort of a phase I trial of adults aged 18-88 years with unresectable or metastatic melanoma with disease progression within 24 weeks of their last dose of ipilimumab, and if BRAF V600 mutation positive, prior treatment with BRAF inhibitor. The trial randomly assigned 173 participants to receive pembrolizumab 2 mg/kg (n=89) or 10 mg/kg (n=84) IV once every 3 weeks until disease progression or unacceptable toxicity, with median follow-up duration of 8 months. Additional inclusion criteria for the study included participants who had progressive, measurable, unresectable melanoma who previously received two or more doses of ipilimumab; with confirmed disease progression using immune-related response; adequate ECOG and organ function; and resolution of ipilimumab-related adverse events. Major study exclusion criteria were "previous treatment with a PD-1 or PD-L1 blocking agent, current systemic immunosuppressive therapy, and active infection or autoimmune disease." Participants were excluded from the study if there was evidence of central nervous system (CNS) progression within 8 weeks of previous treatment. The major efficacy endpoints that were confirmed included overall response rate (ORR) according to Response Evaluation Criteria In Solid Tumors (RECIST v1.1) as assessed by a blinded independent review committee and duration of response (DOR). Both groups had an ORR of 26% with 21 of 81 participants in the 2 mg/kg group and 20 of 76 participants in the 10 mg/kg group (difference 0%, 95% confidence interval [CI], -14 to 13; p=0.96). Safety profiles were similar between groups with treatment well tolerated in this population. There were no drug-related deaths reported. Grade 3 or 4 adverse events occurred in 12% (n=20) of study participants; fatigue was the only drug-related grade 3 to 4 adverse event that occurred in more than 1 participant (n=5 [3%]). Drug-related serious adverse events were reported in 5% (n=8) of the population with 3% (n=6) discontinuing treatment as a result of a drug-related adverse event. Fatigue, pruritus, and rash were the most common drug-related adverse events of any grade reported. In summary Robert and colleagues conclude:

> Our findings suggest that pembrolizumab at a dose of 2 mg/kg or 10 mg/kg every 3 weeks could be an effective treatment option for patients with ipilimumab-refractory advanced melanoma, a population for whom there are few effective treatment options.

The NCCN Drugs and Biologics Compendium™ and the NCCN clinical practice guideline (CPG) in oncology (2017) on melanoma were updated with a Category 1 off-label recommendation for use of pembrolizumab as a single agent for use as first line therapy. The guideline includes a Category 2A recommendation for second-line, subsequent, or re-induction therapy for individuals with a performance status of 0-2. The NCCN CPG states the following:

> Pembrolizumab and nivolumab may cause immune-mediated adverse reactions. Grade 3-4 toxicities are less common than with ipilimumab, but require similar expertise in management. The most common adverse events (>20% of patients) include fatigue, rash, pruritus, cough, diarrhea, decreased appetite, constipation, and arthralgia. Depending on the severity of the reaction, pembrolizumab and nivolumab should be discontinued. For moderate to severe immune-mediated pneumonitis, colitis, hepatitis, hypophysitis, nephritis, and hyperthyroidism anti-PD1 therapy should be discontinued and systemic steroids should be administered. For patients with pre-existent hypophysitis due to

ipilimumab, pembrolizumab may be administered if patients are on appropriate physiologic replacement endocrine therapy.

In 2015, Robert and colleagues reported preliminary results from the KEYNOTE-006 trial, a phase III randomized, open-label, controlled study of 834 participants with histologically confirmed, unresectable stage III or IV melanoma with no more than one previous systemic therapy for advanced disease. The participants were randomly assigned in a 1:1:1 ratio to receive pembrolizumab 10 mg/kg every 2 weeks or pembrolizumab 10 mg/kg every 3 weeks or 4 cycles of ipilimumab 3 mg/kg every 3 weeks. The study inclusion criteria included:

> Known BRAF V600 mutation status was required; previous BRAF inhibitor therapy was not required for patients with normal lactate dehydrogenase levels and no clinically significant tumor-related symptoms or evidence of rapidly progressive disease. Other key eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (on a 5-point scale, with higher scores indicating greater disability) and provision of a tumor sample adequate for assessing PD-L1 expression. Excluded from the study were patients who had received previous therapy with CTLA-4, PD-1, or PD-L1 inhibitors and those who had ocular melanoma, active brain metastases, or a history of serious autoimmune disease. Study results reported:

The estimated 6-month progression-free survival rates were 47.3% for pembrolizumab every 2 weeks, 46.4% for pembrolizumab every 3 weeks, and 26.5% for ipilimumab (hazard ratio for disease progression, 0.58; P<0.001 for both pembrolizumab regimens versus ipilimumab; 95% confidence intervals [CIs], 0.46 to 0.72 and 0.47 to 0.72, respectively). Estimated 12-month survival rates were 74.1%, 68.4%, and 58.2% respectively (hazard ratio for death for pembrolizumab every 2 weeks, 0.63; 95% CI, 0.47 to 0.83; P=0.0005; hazard ratio for pembrolizumab every 3 weeks, 0.69; 95% CI, 0.52 to 0.90; P=0.0036). The response rate was improved with pembrolizumab administered every 2 weeks (33.7%) and every 3 weeks (32.9%), as compared with ipilimumab (11.9%) (P<0.001 for both comparisons).

The rate of Grade 3-5 adverse events were lower in the pembrolizumab group (13.3% and 10.1%) than in the ipilimumab group (19.9%). There were no drug-related deaths in the pembrolizumab group, one drug related death in the ipilimumab group, and common adverse events associated with the use of pembrolizumab were fatigue, diarrhea, rash and pruritus. The authors concluded that the "randomized study comparing two immune checkpoint inhibitors showed that pembrolizumab, as compared with ipilimumab, significantly prolonged progression-free and overall survival with fewer high-grade toxic events in patients with advanced melanoma."

On October 2, 2015, the FDA granted accelerated approval for pembrolizumab to treat individuals with advanced (metastatic) NSCLC whose disease has progressed after other treatment and with tumors that express a protein called PD-L1.

Primary ocular melanoma is treated with radiation, enucleation (eye removal) or transscleral resection depending on the size and location of the tumor.

Non-Small Cell Lung Cancer (NSCLC)
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 24, 2016, the FDA approved expanded use of pembrolizumab as first-line treatment of individuals with metastatic NSCLC whose tumors have high PD-L1 expression (Tumor Proportion Score of 50% or more) with no EGFR or ALK genomic tumor aberrations in nonsquamous carcinoma.

The FDA expanded indication for use of pembrolizumab in individuals with metastatic NSCLC whose tumors express PD-L1 and who have disease progression on or after platinum-containing chemotherapy is based on findings from the Phase I KEYNOTE-001 trial. The safety of pembrolizumab was studied in 550 participants with metastatic NSCLC. The most common side effects reported among study participants included dyspnea, cough, shortness of breath, fatigue, decreased appetite, and severe adverse events resulting from the immune system effect from pembrolizumab. The efficacy for pembrolizumab was demonstrated in a subgroup of 61 participants with pretreated PD-L1 positive advanced NSCLC as determined by the 22C3 pharmDx diagnostic test; the overall response rate for pembrolizumab (percentage of participants who experienced complete and partial shrinkage of their tumors) was 41% (n=25), with effect lasting between 2.1 and 9.1 months. Garon and colleagues reported findings from the KEYNOTE-1, authors conclude that "pembrolizumab had an acceptable side-effect profile and showed antitumor activity in patients with advanced non-small-cell lung cancer. PD-L1 expression in at least 50% of tumor cells correlated with improved efficacy of pembrolizumab".

The FDA approval of expanded use of pembrolizumab as a first-line treatment of individuals with advanced (metastatic) NSCLC was based on preliminary results from the KEYNOTE-024 study, an open-label, phase 3 trial. The study enrolled 305 participants with previously untreated advanced NSCLC with PD-L1 expression on at least 50% of tumor cells and no sensitizing EGFR mutations or ALK translocations to receive pembrolizumab (n=154) or platinum-based chemotherapy (n=151), investigator's choice. The primary end point, "median progression-free survival was 10.3 months (95% confidence interval [CI], 6.7 to not reached) in the pembrolizumab group versus 6.0 months (95% CI, 4.2 to 6.2 in the chemotherapy group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.37 to 0.68; P<0.001)." The pembrolizumab groups rate of overall survival at 6 months was 80.2% versus 72.4% in the chemotherapy group "(hazard ratio for death, 0.60; 95% CI, 0.41 to 0.89; P=0.005)." The pembrolizumab group had a response rate of 44.8%, higher than the 27.8% reported for the chemotherapy group. There were fewer treatment-related adverse events reported of any grade in

the pembrolizumab group (73.4%) versus 90.0% in the chemotherapy group. The rate of Grade 3-5 adverse events were lower in the pembrolizumab group (26.6%) than in the chemotherapy group (53.3%). Reck and colleagues concluded that "in patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, pembrolizumab was associated with significantly longer progression-free and overall survival and with fewer adverse events than was platinum-based chemotherapy."

The updated NCCN Drugs and Biologics Compendium™ and the NCCN clinical practice guideline (CPG) in oncology (2017) on NSCLC offers recommendations for use of pembrolizumab for use as first-line therapy for PD-L1 positive NSCLC with PD-L1 expression positive (≥ 50%) and EGFR, ALK, ROS1 negative or unknown disease (Category 1). The panel includes category 1 recommendations for use of pembrolizumab as a subsequent therapy for disease progression in individuals with NSCLC tumors with PD-L1 expression levels ≥ 1%, when pembrolizumab not previously given. The panel recommendations are based on preliminary results from one phase 1 study (KEYNOTE-001) and a phase 2/3 trial (KEYNOTE-010) that evaluated use of pembrolizumab as subsequent therapy for metastatic NSCLC.

On May 10, 2017, the FDA granted accelerated approval for use of pembrolizumab in combination with pemetrexed and carboplatin as first-line treatment of individuals with untreated metastatic nonsquamous NSCLC. This indication was approved under an accelerated process and is based upon unpublished data from the phase I/II KEYNOTE-021 trial (Cohort G1), an open-label, multicenter, multi-cohort study that evaluated tumor response and progression-free survival in 74 individuals with nonsquamous NSCLC. The FDA also included a contingency that continued approval may be based upon verification and description of clinical benefit in confirmatory trials. According to the Keytruda product label, "in Cohort G1 of KEYNOTE-021, there was a statistically significant improvement in ORR in patients randomized to Keytruda in combination with pemetrexed and carboplatin compared with pemetrexed and carboplatin alone." Langer and colleagues reported early findings from a phase 2 cohort of the multi-cohort KEYNOTE-021 open-label trial.

Head and Neck Cancer

On August 5, 2016, Merck Sharp & Dohme Corp. was granted FDA approval for pembrolizumab for use in the treatment of individuals with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. The accelerated approval was based on data from the KEYNOTE-012 study, a multicenter, nonrandomized, open-label phase 1b study that evaluated safety in 192 participants with recurrent or metastatic HNSCC with ECOG performance status of 0 to 1. Efficacy was evaluated in 174 of the participants with disease progression on or after receiving platinum-containing chemotherapy (as induction, concurrent, or adjuvant therapy). Pembrolizumab was administered at 10 mg/kg every 2 weeks (n=53) or 200 mg every 3 weeks (n=121) until unacceptable toxicity or rapid disease progression that was symptomatic, requiring urgent intervention. Participants without disease progression received treatment with pembrolizumab for a period up to 24 months. The pembrolizumab (Keytruda) 2017 FDA Product Information label product label reported study response rates:

> The ORR was 16% (95% CI: 11, 22) with a complete response rate of 5%. The median follow-up time was 8.9 months. Among the 28 responding patients, the median duration of response had not been reached (range 2.4+ to 27.7+ months), with 23 patients having responses of 6 months or longer. The ORR and duration of response were similar irrespective of dosage regimen (10mg/kg every 2 weeks or 200mg every 3 weeks) or HPV status.

The NCCN Drugs and Biologics Compendium and the NCCN CPG in oncology (2017) on head and neck cancer include Category 2A off-label recommendations for use of pembrolizumab as a treatment of recurrent, unresectable or metastatic disease HNSCC (non-nasopharyngeal) as a single agent for disease progression on or after platinum-containing chemotherapy based on panel consensus and preliminary findings reported from two phase Ib studies.

Hodgkin Lymphoma
In March 2017 the FDA granted expanded use of pembrolizumab in the treatment of adults or children with refractory classic Hodgkin lymphoma (cHL), or in the treatment of individuals who have relapsed after three or more prior lines of therapy. The National Comprehensive Cancer Network® (NCCN) Drugs and Biologics Compendium™ and the NCCN CPG for Hodgkin disease (2017) includes a 2A recommendation for off-label use of pembrolizumab as an additional therapy option when used as a single agent for individuals with relapsed or refractory cHL. The recommendation is based on uniform consensus and data from a phase Ib study (KEYNOTE-013) of individuals with relapsed or refractory cHL treated with pembrolizumab after brentuximab vedotin failure; 67% of participants also failed prior autologous stem cell transplant. There were no serious adverse events reported among participants. A total of 3 participants (20%) had a complete response (CR) at 12 weeks. "Five additional patients (33%) had partial remission as best overall response, for an overall response rate of 53%. Four patients (27%) experienced PD, although all 4 experienced a decrease in their overall tumor burden." The authors concluded that "pembrolizumab therapy appears to be safe, tolerable, and associated with clinical benefit in patients with heavily pretreated cHL."

Merkel Cell Carcinoma
Nghiem and colleagues (2016) reported preliminary results from a multicenter, phase 2, noncontrolled study of 26 adults with the rare condition advanced Merkel cell carcinoma, in which subjects received pembrolizumab as first-line therapy with a median follow-up of 33 weeks. Efficacy was evaluated in 25 participants that received one or more evaluations during treatment. Authors observed an ORR of 56% (95% CI, 35 to 76); 4 participants had a complete response rate and 10 had a partial response. "The rate of progression-free survival at 6 months was 67% (95% CI, 49 to 86)". Grade 3 to 4 drug-related adverse events were observed in 15% of participants. Authors conclude that:

> Although additional experience with longer follow-up and larger patient cohorts is needed, these early findings compare favorably with results for standard chemotherapy regimens for this tumor, for which retrospective studies show a median progression-free survival of approximately 3 months, with progressive disease developing in 90% of patients within 10 months.

In the NCCN Drugs and Biologics Compendium and the NCCN CPG in Oncology on Merkel cell carcinoma (2017), the panel included a category 2A recommendation for off-label use of pembrolizumab in the treatment of disseminated disease as clinical judgment dictates; the "preliminary data from non-randomized trials in patients with MCC demonstrate that response rates of durable response are improved with PD-1/PD-L1 blockade compared with cytotoxic therapy.".

Colorectal Cancer
Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. Approximately 50% to 60% of patients diagnosed with colorectal cancer develop colorectal metastases, and 80% to 90% of these patients have unresectable metastatic liver disease. Metastatic disease most frequently develops metachronously after treatment for locoregional colorectal cancer, with the liver being the most common site of involvement. However, 20% to 34% of patients with colorectal cancer presents with synchronous liver metastases.

In March 2017, the NCCN Drugs and Biologics Compendium and the NCCN CPG in Oncology on colon cancer and rectal cancer list off-label use of pembrolizumab for individuals with unresectable metachronous metastases or unresectable advanced or metastatic colorectal cancer. The recommendations were based on 2A category of evidence and uniform consensus. The panel recommends:

> Use of pembrolizumab or nivolumab as treatment options in patients with metastatic MMR-deficient colorectal cancer in second- or third-line therapy. Patients progressing on either of these drugs should not be offered the other. Additional clinical trials are ongoing to confirm the benefit of these drugs in this setting.

On May 23, 2017, the FDA granted accelerated approval for expanded use of pembrolizumab in adults or children for the treatment of unresectable or metastatic solid tumors (dMMR/MSIH only) with disease progression following prior treatment and no other satisfactory alternative treatment options identified. The approval included coverage in treatment of individuals with unresectable or metastatic colorectal cancer (dMMR/MSIH only) with disease progression following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. The FDA approval was based on tumor response rate and durability of response. The FDA also included a contingency that continued approval may be based upon verification and description of clinical benefit in confirmatory trials.

Urothelial Carcinoma
Merck Sharp & Dohme Corp. was granted regular FDA approval on May 18, 2017 for use of pembrolizumab in the treatment of individuals with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. On May 18, 2017 the FDA also granted accelerated approval for use of pembrolizumab in the treatment of individuals with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy. The regular FDA approval for second-line indication was based on preliminary data from the KEYNOTE-045

trial, a multicenter, randomized, active-controlled trial in individuals with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum-containing chemotherapy. Individuals were randomly assigned at a 1:1 ratio to the pembrolizumab group 200 mg every 3 weeks (n=270) or investigator's choice of a chemotherapy regimen (paclitaxel [n=84], docetaxel [n=84], or vinflunine [n=87]) every 3 weeks (n=272). According to the FDA press release:

> The trial demonstrated statistically significant improvements in overall survival (OS) and objective response rate (ORR) for participants assigned to pembrolizumab as compared to chemotherapy. Median OS was 10.3 and 7.4 months in the pembrolizumab and chemotherapy arms, respectively (HR 0.73; 95% CI: 0.59, 0.91, p=0.004). ORR was 21% for pembrolizumab and 11% for chemotherapy (p=0.002). No statistically significant difference in progression-free survival between the two arms was observed.
>
> The accelerated approval for the first-line indication was based on data from KEYNOTE-052, a single-arm, open-label trial in 370 patients with locally advanced or metastatic urothelial carcinoma who were deemed not eligible for cisplatin-containing chemotherapy. Patients received pembrolizumab 200 mg every 3 weeks. With a median follow-up time of 7.8 months, the ORR was 28.6% (95% CI 24, 34) and the median response duration was not reached (range 1.4+, 17.8+ months).
>
> The most common adverse reactions reported for at least 20% of pembrolizumab-treated patients in either of the two trials included fatigue, musculoskeletal pain, pruritus, decreased appetite, nausea, diarrhea, constipation, and rash. Discontinuation of pembrolizumab secondary to adverse reactions occurred in 8% of participants in KEYNOTE-045 and in 11% in KEYNOTE-052. Dose interruption of pembrolizumab occurred in approximately 20% of patients in either trial. Serious adverse reactions occurred in approximately 40% of pembrolizumab-treated patients. Immune-mediated adverse reactions, including pneumonitis, colitis, hepatitis, and endocrinopathies, were reported in the trials and were managed according to guidelines in Warnings and Precautions of the label.

Gastric Cancer
Pembrolizumab is recommended for dMMR/MSI-high advanced gastric cancers as a second- or subsequent-line treatment option. In addition, pembrolizumab has also been granted accelerated approval by the FDA for the treatment of patients with recurrent locally advance or metastatic gastric adenocarcinoma whose tumors express PD-L1 (combined positive score ≥ 1), as a third or subsequent-line therapy option.

The approval was based on results of the KEYNOTE-059 study, an open label, multicenter, non-comparative, phase 2 trial. Cohort 1 of this trial included 259 patients with gastric or EGJ adenocarcinoma who had progressed on two or more prior lines of therapy. 57.1 % of these patients (n=143) had PD-L1 positive tumors. Of those with PD-L1 positive tumors, overall ORR was 15.5% (95% Cl, 10.1 – 22.4), with 2% (95% Cl, 0.4-5.8) of patients achieving a complete response.

Key Words:

Metastatic melanoma, Non-small cell lung cancer (NSCLC), Keytruda, pembrolizumab, head and neck squamous cell carcinoma (HNSCC), Hodgkin lymphoma, Merkel cell carcinoma, bladder cancer, urothelial carcinoma, microsatellite instability-high cancer, gastric cancer, colorectal cancer, gastroesophageal cancer,

Approved by Governing Bodies:

On September 4, 2014, the U.S. Food and Drug Administration (FDA) granted accelerated approval to Keytruda (pembrolizumab) for treatment of patients with advanced or unresectable melanoma who are no longer responding to other drugs.

On October 2, 2015, the FDA granted accelerated approval for pembrolizumab to treat individuals with advanced (metastatic) NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy.

On August 5, 2016, the FDA granted accelerated approval to pembrolizumab for the treatment of individuals with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.

On October 24, 2016, the FDA approved pembrolizumab (Keytruda, Merck & Co., Inc.) for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by an FDA-approved test.

On March 14, 2017, the FDA granted accelerated approval to pembrolizumab (Keytruda, Merck & Co., Inc.) for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or those who have relapsed after three or more prior lines of therapy.

May 10, 2017, the FDA granted accelerated approval to pembrolizumab in combination with pemetrexed and carboplatin for the treatment of patients with previously untreated metastatic non-squamous non-small cell lung cancer (NSCLC)

On May 18, 2017, the FDA granted regular approval to pembrolizumab for patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

On May 23, 2017, the FDA granted accelerated approval to pembrolizumab for adults and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

On September 22, 2017, the FDA granted accelerated approval to pembrolizumab for patients with recurrent locally advanced metastatic, gastric, or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 as determined by an FDA-approved test. Patients must have had disease progression in or after two or more prior systemic therapies, including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2neu-targeted therapy.

Benefit Application:

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

Current Coding:

CPT Codes:

J9271 Injection, pembrolizumab, 1 mg

References:

1. American Cancer Society. Cancer facts & figures 2017. Atlanta: American Cancer Society; 2017.
2. American Cancer Society. www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-key-statistics.
3. Arkenau HT, Kefford R, Long GV. Targeting BRAF for patients with melanoma. Br J Cancer. 2011; 104(3):392-398.
4. Armand P, Shipp MA, Ribrag V, et al. Programmed death-1 blockage with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. J Clin Oncol. 2016; 34(31):3733-3739.
5. Bellmunt J, deWit R, Vaugh DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Eng J Med. 2017; 376(11):1015-1026.
6. Chapman PB, Hauschild A, Sondak VK. Frontline Approach to Metastatic BRAF-Mutant Melanoma Diagnosis, Molecular Evaluation, and Treatment Choice. Asco.org/edbook.
7. Chow LQ, Haddad R, Gupta S, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase lb KEYNOTE-012 expansion cohort. J Clin Oncol. 2016.
8. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature. 2002; 417(6892):949-954.
9. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: globocan.iarc.fr.
10. Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med. 2010; 363(9):809-819.
11. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015; 372(21):2018-2028.
12. Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (Anti-PD-1) in Melanoma. N Engl J Med. 2013; 369(2):134-144.

13. Keytruda [Product Information]. Whitehouse Station, NJ. Merck Sharp & Dohme Corp.; December 18, 2015. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2015/125514s004s006lbl.pdf.
14. Keytruda prescribing information. Merck & Co. September 2014.
15. Khan MA, Andrews S, Ismail-Khan R, et al. Overall and progression-free survival in metastatic melanoma: analysis of a single-institution database. Cancer Control. 2006; 13(3):211-217.
16. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small cell lung cancer: a randomized, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet. 2016; 17:1497-1508.
17. Merck Sharp & Dohme Corp. A trial of pembrolizumab (MK-3475) in participants with blood cancers (MK-3475-013)(KEYNOTE-013). NLM Identifier: NCT01953692. Last updated April 26, 2016. Available at: clinicaltrials.gov/ct2/show/NCT01953692.
18. Merck Sharp & Dohme Corp. Study of pembrolizumab (MK-3475) in participants with progressive locally advanced or metastatic carcinoma, melanoma, or non-small cell lung carcinoma (P07990/MK-3475-001/KEYNOTE-001). NLM Identifier: NCT01295827. Last updated on February 3, 2016. Available at: clinicaltrials.gov/ct2/show/NCT01295827?term=01295827&rank=1.
19. Moskowitz CH, Ribrag V, Michot J-M, et al. PD-1 blockade with the monoclonal antibody pembrolizumab (MK-3475) in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: preliminary results form a phase 1b study (KEYNOTE-013) [abstract]. Blood 2014; 124: Abstract 290.
20. National Cancer Institute. Common terminology criteria for adverse events. Version 4.03. June 2010. Available at: evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.
21. National Cancer Institute. Surveillance, Epidemiology, and End Results Program (SEER). Available at: seer.cancer.gov/statfacts/html/lungb.html.
22. National Cancer Institute. Pembrolizumab secures FDA approval in stomach cancer. Oct 12, 2017. Available at: www.cancer.gov/news-events/cancer-currents-blog/2017/gastric-cancer-fda-keytruda.
23. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines on Oncology. Bladder Cancer. Version 5.2017. Available at: www.nccn.org.
24. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines on Oncology. Colon Cancer. Version 2.2017. Available at: www.nccn.org.
25. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines on Oncology. Gastric Cancer. Version 5.2017. Available at: www.nccn.org.
26. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines on Oncology. Head and Neck Cancers. Version 2.2017. Available at: www.nccn.org.
27. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines on Oncology. Hodgkin lymphoma. Version 1.2017. Available at: www.nccn.org.
28. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology. Melanoma. Version 1.2018. Available at: www. nccn.org.
29. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines on Oncology. Merkel Cell Carcinoma. Version 1.2017. Available at: www.nccn.org.
30. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 1.2018. Available at: www.nccn.org.

31. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines on Oncology. Rectal Cancer. Version 3.2017. Available at: www.nccn.org.
32. National Comprehensive Cancer Network®. NCCN Categories of Evidence and Consensus. Available at: //www.nccn.org/professionals/physician_gls/categories_of_consensus.asp.
33. National Comprehensive Cancer Network®. NCCN Drugs & Biologic Compendium™ (electronic version). For additional information visit the NCCN website: www.nccn.org
34. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. N Engl J Med. 2016; 374(26):2542-2552.
35. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative oncology Group. Am J Clin Oncol. 1982; 5(6):649-655.
36. Pembrolizumab. Clinicaltrials.gov. Available at: www.clinicaltrials.gov/ct2/results?term=pembrolizumab+and+ipilimumab.
37. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Eng J Med. 2016 Oct 8.
38. Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomized dose-comparison cohort of a phase 1 trial. Lancet. 2014; 384(9948):1109-1117.
39. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015; 372(26):2521-2532.
40. Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicenter, phase 1b trial. Lancet Oncol. 2016; (7):956-965.
41. Shahabi V, Whitney G, Hamid O, et al. Assessment of association between BRAF-V600E mutation status in melanomas and clinical response to ipilimumab. Cancer Immunol Immunother. 2012; 61(5):733-737.
42. Treatment of primary ocular melanoma. Available at: www.cancer.gov/cancertopics/pdq/treatment/intraocularmelanoma/HealthProfessional/page4.

Policy History:

New policy created January 2015, effective date September 1, 2015
Medical Policy Group, September 2016
Available for comment September 21, 2016 to November 5, 2016
Medical Policy Group, April 2017
Medical Policy Group December 2017
Available for comment December 12, 2017 to January 26, 2018
Medical Policy Group, November 2018