Clinical Policy: Pembrolizumab (Keytruda)

Reference Number: CP.PHAR.322
Effective Date: 03.01.17
Last Review Date: 11.17
Line of Business: Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Pembrolizumab (Keytruda®) is a programmed death receptor-1 (PD-1)-blocking antibody.

FDA Approved Indication(s)

Keytruda is indicated for the treatment of:

- Melanoma
  - For the treatment of patients with unresectable or metastatic melanoma.
- Non-Small Cell Lung Cancer (NSCLC)
  - As a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [(Tumor Proportion Score (TPS) ≥50%)] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.
  - As a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after 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 Keytruda.
  - In combination with pemetrexed and carboplatin, as first-line treatment of patients with metastatic nonsquamous NSCLC.*
- Head and Neck Squamous Cell Cancer (HNSCC)
  - For the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.*
- Classical Hodgkin Lymphoma (cHL)
  - For the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy.*
- Urothelial Carcinoma
  - For the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.*
  - For the treatment of 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.
- Microsatellite Instability-High Cancer
  - For the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient*
    - Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or

    - Colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
  - Limitation(s) of use: The safety and effectiveness of Keytruda in pediatric patients with MSI-H central nervous system cancers have not been established
- Gastric Cancer
  - For the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.*

* This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Policy/Criteria
Provider must submit documentation (which may include office chart notes and lab results) supporting that member has met all approval criteria

It is the policy of health plans affiliated with Centene Corporation® that Keytruda is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Melanoma (must meet all)**:**
1. Diagnosis of unresectable or metastatic melanoma;
2. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

B. Non-Small Cell Lung Cancer (must meet all)**:**
1. Diagnosis of NSCLC;
2. Disease is recurrent or metastatic;
3. Meets one of the following (a or b):
   a. FDA-approved use (i or ii):
      i. First-line therapy (a or b):
         a) Disease is non-squamous and metastatic, and Keytruda is prescribed in combination with pemetrexed and carboplatin;
         b) Tumor PD-L1 expression ≥ 50% (Tumor Proportion Score [TPS]), and EGFR and ALK mutation status negative or unknown;
      ii. Subsequent therapy (a and b):
         a) Tumor PD-L1 expression ≥ 1% (TPS);
         b) Disease has progressed on or after (1, 2, or 3):
            1) Platinum containing chemotherapy if EGFR and ALK mutation status negative or unknown;

2) FDA-approved therapy if EGFR mutation status is positive (e.g., erlotinib, afatinib, gefitinib, osimertinib);
3) FDA-approved therapy if ALK mutation status is positive (e.g., crizotinib, ceritinib, alectinib, brigatinib);

b. Off-label NCCN recommended use (i or ii):
i. First-line therapy (a and b):
a) Tumor PD-L1 expression ≥ 50% (TPS);
b) ROS1 mutation status negative or unknown;
ii. Subsequent therapy (a or b):
a) Tumor PD-L1 expression ≥ 50% (TPS) and (1):
1) ROS1 mutation status positive and member has received crizotinib therapy;
b) Tumor PD-L1 expression ≥ 1% (TPS) and systemic immune checkpoint inhibitors have not yet been given (e.g., nivolumab, pembrolizumab, atezolizumab) and (1 or 2):
1) Following progression on a first-line cytotoxic regimen (first-line regimens not limited to platinum-containing chemotherapy);
2) For further progression on other systemic therapy;

4. Request meets one of the following (a or b):
a. Dose does not exceed 200 mg every 3 weeks;
b. Requested dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

C. Head and Neck Squamous Cell Carcinoma (must meet all)**:**
1. Diagnosis of head and neck squamous cell carcinoma (HNSCC) (*see Appendix B* for subtypes by location);
2. Disease has progressed on or after platinum-containing chemotherapy;
3. Meets one of the following (a or b):
a. FDA-approved use:
i. Disease is recurrent or metastatic;
b. Off-label NCCN recommended use:
i. Prescribed as a single agent for non-nasopharyngeal cancer and one of the following (a, b, or c):
a) Disease or other factors preclude surgery;
b) Very advanced (T4b*) nonmetastatic disease;
c) Unresectable disease with one of the following characteristics (1 or 2):
1) Nodal disease with no metastases;
2) Second primary tumor and member has received prior radiation therapy;

2. Request meets one of the following (a or b):
a. Dose does not exceed 200 mg every 3 weeks;
b. Requested dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**American Joint Committee on Cancer () TNM staging classification (7th ed., 2010) as reported in NCCN Head and Neck Cancers: T (primary tumor characteristics); N (regional lymph nodes); M (metastatic disease).*

Approval duration: 6 month

D. Classical Hodgkin Lymphoma (must meet all):
1. Diagnosis of classical Hodgkin lymphoma (cHL);
2. Meets one of the following (a or b):
   a. FDA approved use (i or ii):
      i. Disease is refractory (defined as disease that does not improve or go away in response to treatment);
      ii. Member has relapsed (defined as worsening or return of cancer after a period of improvement) after 3 or more prior lines of therapy;
   b. Off-label NCCN recommended use (i or ii):
      i. Age ≥ 18 years, and member has relapsed after treatment with brentuximab vedotin;
      ii. Age > 60 years, and Keytruda will be used as palliative therapy for relapsed disease;
3. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg (2 mg/kg [maximum 200 mg] if age < 18 years) every 3 weeks;
   b. Requested dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

E. Urothelial Carcinoma (must meet all):
1. Diagnosis of urothelial carcinoma;
2. Disease is locally advanced, recurrent, or metastatic;
3. Meets one of the following (a or b):
   a. FDA approved use (i or ii):
      i. Member is not eligible for cisplatin-containing chemotherapy;
      ii. Disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy;
   b. Off-label NCCN recommended use:
      i. As a single agent for subsequent systemic therapy (e.g., atezolizumab or gemcitabine-containing chemotherapy);
4. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks;
   b. Requested dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

F. Microsatellite Instability-High Cancer (must meet all):
1. Diagnosis of MSI-H or defective mismatch repair (dMMR) cancer;

2. Disease is unresectable or metastatic;
3. Meets one of the following (a or b):
   a. Colorectal cancer (*colon cancer, rectal cancer, or both*) (i or ii):
      i. FDA approved use:
         a) Disease progressed following treatment with a fluoropyrimidine (e.g., fluorouracil, capecitabine), oxaliplatin, and irinotecan;
      ii. Off-label NCCN recommended use (a or b):
         a) Previous adjuvant therapy with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months;
         b) As a single agent for patients with advanced or metastatic disease who are not appropriate for intensive therapy;
   b. Other solid tumors (*see Appendix C for examples*) (i and ii):
      i. Disease progressed following prior treatment;
      ii. Documentation supports lack of satisfactory treatment alternatives;
4. Request meets one of the following (a or b):
   c. Dose does not exceed 200 mg (2 mg/kg [maximum 200 mg] if age < 18 years) every 3 weeks;
   d. Requested dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

G. Gastric Cancer (must meet all):
1. Diagnosis of recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma;
2. Tumors express PD-L1 [Combined Positive Score (CPS) ≥1];
3. Progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy;
4. Request meets any of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

Approval duration: 6 months

H. Other diagnoses/indications
1. Refer CP.PHAR.57 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a, b, or c):

a. Melanoma, NSCLC, HNSCC, urothelial carcinoma, or gastric cancer: new dose does not exceed 200 mg every 3 weeks;
b. cHL or MSI-H cancer: new dose does not exceed 200 mg every 3 weeks;
c. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to CP.PHAR.57 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – CP.PHAR.57 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALK: anaplastic lymphoma receptor
cHL: classical Hodgkin lymphoma
CPS: Combined positive score
dMMR: mismatch repair deficient
EGFR: epidermal growth factor receptor
FDA: Food and Drug Administration
HNSCC: head and neck squamous cell carcinoma
MSI-H: microsatellite instability-high
NCCN: National Comprehensive Cancer Network
NSCLC: non-small cell lung cancer
PD-1: programmed cell death protein 1
PD-L1/2: programmed death-ligand 1/2
ROS1: ROS proto-oncogene 1, receptor tyrosine kinase
TPS: tumor proportion score

Appendix B: Head and Neck Squamous Cell Cancers by Location[*5]

- Paranasal sinuses (ethmoid, maxillary)
- Larynx (glottis, supraglottis)
- Pharynx (nasopharynx, oropharynx, hypopharynx)
- Lip and oral cavity
- Major salivary glands (parotid, submandibular, sublingual)
- Occult primary

**Squamous cell carcinoma, or a variant, is the histologic type in more than 90% of head and neck cancers.*

Appendix C: Examples of Solid Tumors

- Endometrial cancer
- Biliary cancer
- Gastric/gastroesophageal junction cancer
- Pancreatic cancer

- Small intestinal cancer
- Breast cancer
- Prostate cancer
- Bladder cancer
- Esophageal cancer
- Sarcoma
- Thyroid cancer
- Retroperitoneal adenocarcinoma
- Small cell lung cancer
- Renal cell carcinoma

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Melanoma	200 mg IV every 3 weeks	200 mg every 3 weeks
NSCLC	200 mg IV every 3 weeks	200 mg every 3 weeks
HNSCC	200 mg IV every 3 weeks	200 mg every 3 weeks
cHL	200 mg IV every 3 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics	200 mg every 3 weeks
Urothelial Carcinoma	200 mg IV every 3 weeks	200 mg every 3 weeks
MSI-H Cancer	200 mg IV every 3 weeks for adults and 2 mg/kg (up to 200 mg) every 3 weeks for children.	200 mg every 3 weeks
Gastric or gastroesophageal junction adenocarcinoma	200 mg IV every 3 weeks	200 mg every 3 weeks

All regimens are an intravenous infusion over 30 minutes

VI. Product Availability

Single-dose vial: 50 mg lyophilized powder for reconstitution, 100 mg/4 mL (25 mg/mL) solution

VII. References

1. Keytruda Prescribing Information. Whitehouse Station, NJ: Merck and Co.; May 2017. Available at http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf. Accessed October 2, 2017.
2. Pembrolizumab. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed October 6, 2017.
3. Melanoma (Version 1.2017). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed January 23, 2017.
4. Non-small cell lung cancer (Version 6.2017). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed May 18, 2017.
5. Head and neck cancers (Version 2.2016). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed January 23, 2017.
6. Hodgkin lymphoma (Version 1.2017). In: National Comprehensive Cancer Network Guidelines. Available at www.NCCN.org. Accessed May 2, 2017.

7. Bladder cancer (Version 5.2017). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed May 25, 2017.
8. Dictionary. In: National Comprehensive Cancer Network Patient and Caregiver Resources. Available at https://www.nccn.org/patients/resources/dictionary/. Accessed June 8, 2017.
9. Gastric Cancer (Version 4.2017). In: National Comprehensive Cancer Network Guidelines. Available at www. NCCN.org. Accessed October 9, 2017.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy split from CP.PHAR.182 Excellus Oncology. Non-small cell lung cancer: NCCN off-label recommendations added; "recurrent or" added to "metastatic disease" and "or unknown" added to "negative mutation status" to consolidate criteria of those FDA/NCCN uses that differed by the referenced terms. Head and neck cancers: NCCN off-label recommended uses added; subtypes by location outlined at Appendix B.	01.17	03.17
Created criteria for new FDA indications: cHL, urothelial carcinoma, and MSI-H cancer. Melanoma: modified max dose from 2 mg/kg to 200 mg per package insert. NSCLC: added criteria for updated FDA indication (non-squamous metastatic disease). HNSCC: specified that recommended NCCN off-label uses pertain to non-nasopharyngeal cancer. All indications: added max dose requirement to both initial and re-auth criteria. Increased all approval durations from 3/6 months to 6/12 months. Removed reasons to discontinue. Added requirement for documentation of positive response to therapy.	05.17	08.17
Created criteria for new FDA indications per PI and NCCN: Gastric Cancer	10.17	11.17

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.