Clinical Policy: Pembrolizumab (Keytruda)

Reference Number: PA.CP.PHAR.322
Effective Date: 01/18
Last Review Date: 07/18

Coding Implications
Revision Log

Description
The intent of the criteria is to ensure that patients follow selection elements established by Pennsylvania Health and Wellness ® clinical policy for pembrolizumab for injection (Keytruda®).

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
It is the policy of Pennsylvania Health and Wellness ® 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 non-small cell lung cancer (NSCLC);
2. Disease is recurrent or metastatic;
3. Meets 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);
   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 and BRAF mutation status negative or unknown;

ii. Subsequent therapy and (a or b):
a) Tumor PD-L1 expression ≥ 50% (TPS) (1) :
1) ROS1 and BRAF negative or unknown;
b) Tumor PD-L1 expression ≥1% (TPS) and systemic immune checkpoint inhibitors have not yet been given (e.g., nivolumab, pembrolizumab, atezolizumab) (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.

2. 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 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 (a, b or c):
a) Disease or other factors preclude surgery;
b) Very advanced (T4b*) nonmetastatic disease;
c) Unresectable disease with the following characteristics (1 or 2):
1) Nodal disease with no metastases;
2) Second primary tumor and member has received prior radiation therapy.
4. 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*).

**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 months

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 or refractory 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 - (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: Refer to CP.PMN.53.

II. Continued Approval

A. All Indications (must meet all)**:**

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PA.01) applies;
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 Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PA.01) applies; or
2. Refer to PA.CP.PMN.53

Background

Description/Mechanism of Action:

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

Formulations:

Keytruda for injection is supplied as follows:
- Lyophilized powder:
  - 50 mg single-use vial; concentration of 25 mg/mL after reconstitution
- Solution:
  - 100 mg/4 mL (25 mg/mL), single-use vial

Appendices

Appendix A: Abbreviation Key

ALK: Anaplastic lymphoma receptor
EGFR: Epidermal growth factor receptor
HNSCC: Head and neck squamous cell carcinoma
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.*

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes
J9271

Reviews, Revisions, and Approvals	Date	Approval Date
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. References reviewed and updated.	02/18	

References
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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.
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