# Clinical Policy: Pembrolizumab (Keytruda)

Reference Number: CP.PHAR.322
Effective Date: 03.01.17
Last Review Date: 05.20
Line of Business: Commercial, HIM, Medicaid

Coding Implications
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:

- **Melanoma**
  - For the treatment of patients with unresectable or metastatic melanoma.
  - For the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.
- **Non-small cell lung cancer (NSCLC)**
  - In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations.
  - In combination with carboplatin and either paclitaxel or nab-paclitaxel, as first-line treatment of patients with metastatic squamous NSCLC.
  - As a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥ 1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:
    - Stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
    - Metastatic.
  - 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.
- **Small cell lung cancer (SCLC)**
  - For the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.*
- **Head and neck squamous cell cancer (HNSCC)**
  - In combination with platinum and fluorouracil (FU) for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.
  - As a single agent for the first line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test.
  - As a single agent 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.*
- **Primary mediastinal large B-cell lymphoma (PMBCL)**
  - For the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy.*
  - Limitation(s) of use: Keytruda is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.
- **Urothelial carcinoma**
  - For the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.*
  - 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.
  - For the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.
- **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 (dMMR)*
    - 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 (esophagogastric junction; EGJ) adenocarcinoma whose tumors express PD-L1 (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, human epidermal growth factor receptor 2 (HER2)/neu-targeted therapy.*
- **Esophageal cancer**
  - For the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.
- **Cervical cancer**
  - For the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.*

- **Hepatocellular carcinoma (HCC)**
  - For the treatment of patients with HCC who have been previously treated with sorafenib*
- **Merkel cell carcinoma (MCC)**
  - For the treatment of adult and pediatric patients with recurrent locally advanced or metastatic MCC.*
- **Renal cell carcinoma (RCC)**
  - For use in combination with axitinib for the first-line treatment of patients with advanced RCC.
- **Endometrial carcinoma (EC)**
  - In combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.*

** 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.*

**Contents:**



**Policy/Criteria**

*Provider must submit documentation (such as office chart notes, lab results or other clinical information) 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 melanoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is lymph node positive, recurrent, unresectable, or metastatic;
5. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks (for a maximum of 12 months if adjuvant treatment);
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

**Approval duration:**
**Medicaid/HIM** – 6 months
**Commercial** – 6 months or to the member's renewal date, whichever is longer

**B. Non-Small Cell Lung Cancer** (must meet all)**:**

1. Diagnosis of NSCLC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is recurrent, advanced, or metastatic;
5. If disease is positive for an EGFR, ALK, or ROS1 mutation, disease has progressed on or after targeted therapy *(see Appendix B for examples of targeted therapy);*
6. Request is for one of the following (a, b, or c):
   a. Tumor expresses PD-L1 (TPS ≥ 1%);
   b. Keytruda is prescribed as first-line therapy in combination with a chemotherapy regimen *(see Appendix B for examples of combination therapy)*;
   c. Keytruda is prescribed as single-agent therapy for brain metastasis;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

**Approval duration:**
**Medicaid/HIM** – 6 months
**Commercial** – 6 months or to the member's renewal date, whichever is longer

**C. Small Cell Lung Cancer** (must meet all)**:**

1. Diagnosis of SCLC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is unresectable or metastatic;
5. Disease has progressed on or after platinum-based chemotherapy (e.g., cisplatin, carboplatin);

6. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

**Approval duration:**
**Medicaid/HIM** – 6 months
**Commercial** – 6 months or to the member's renewal date, whichever is longer

**D. Head and Neck Squamous Cell Carcinoma** (must meet all)**:**
1. Diagnosis of HNSCC *(locations include paranasal sinuses, larynx, pharynx, lip, oral cavity, salivary glands; may be occult primary - i.e., primary source unknown)*;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is unresectable, recurrent, or metastatic;
5. Meets one of the following (a, b, or c):
   a. Keytruda is requested as first-line therapy in combination with platinum-containing chemotherapy and FU;
   b. Keytruda is requested as a first-line single agent and the tumor expresses PD-L1 with a CPS of ≥ 1;
   c. Keytruda is requested as a single agent for disease that has progressed on or after platinum-containing chemotherapy (e.g., cisplatin, carboplatin);
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

**Approval duration:**
**Medicaid/HIM** – 6 months
**Commercial** – 6 months or to the member's renewal date, whichever is longer

**E. Classical Hodgkin Lymphoma** (must meet all)**:**
1. Diagnosis of cHL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 2 years;
4. Disease is refractory to ≥ 1 line of therapy or has relapsed after ≥ 3 lines of therapy *(a line of therapy may include systemic therapy or transplantation; see Appendix B for examples of systemic therapy)*;
5. Request meets one of the following (a, b, or c):*
   a. Adults: Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Pediatrics: Dose does not exceed 2 mg/kg (up to 200 mg) every 3 weeks for a maximum of 24 months;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

**Approval duration:**

**Medicaid/HIM** – 6 months
**Commercial** – 6 months or to the member's renewal date, whichever is longer

**F. Primary Mediastinal Large B-Cell Lymphoma** (must meet all)**:**
1. Diagnosis of PMBCL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 2 years;
4. Disease is refractory to or has relapsed after ≥ 1 line of therapy *(a line of therapy may include systemic therapy or transplantation; see Appendix B for examples of systemic therapy)*;
5. Request meets one of the following (a, b, or c):*
   a. Adults: Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Pediatrics: Dose does not exceed 2 mg/kg (up to 200 mg) every 3 weeks for a maximum of 24 months;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

**Approval duration:**
**Medicaid/HIM** – 6 months
**Commercial** – 6 months or to the member's renewal date, whichever is longer

**G. Urothelial Carcinoma** (must meet all)**:**
1. Diagnosis of urothelial carcinoma;
2. Prescribed by or in consultation with an oncologist or urologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a or b):
   a. For locally advanced or metastatic disease, member is ineligible for or has previously received platinum-containing chemotherapy (e.g., cisplatin, carboplatin);
   b. For BCG-unresponsive, high-risk, NMIBC with CIS, member is ineligible for or has elected not to undergo cystectomy;
5. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

**Approval duration:**
**Medicaid/HIM** – 6 months
**Commercial** – 6 months or to the member's renewal date, whichever is longer

**H. Microsatellite Instability-High/Mismatch Repair Deficient Cancer** (must meet all)**:**
1. Diagnosis of a solid tumor classified as MSI-H or dMMR (indicative of MMR gene mutation or loss of expression) *(see Appendix D for examples of solid tumors)*;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 2 years;

4. Keytruda is prescribed as subsequent therapy for solid tumors other than colorectal cancer, gallbladder cancer, or intrahepatic/extrahepatic cholangiocarcinoma;
5. Request meets one of the following (a or b):*
   a. Adults: Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Pediatrics: Dose does not exceed 2 mg/kg (up to 200 mg) every 3 weeks for a maximum of 24 months;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

**Approval duration:**
**Medicaid/HIM** – 6 months
**Commercial** – 6 months or to the member's renewal date, whichever is longer

**I. Gastric, EGJ, and Esophageal Adenocarcinoma** (must meet all)**:**
1. Diagnosis of gastric, EGJ, or esophageal adenocarcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is unresectable, locally advanced, recurrent, or metastatic;
5. Tumor expresses PD-L1 (CPS ≥ 1);
6. Disease has progressed on or after ≥ 2 lines of systemic therapy *(see Appendix B for examples)*;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

**Approval duration:**
**Medicaid/HIM** – 6 months
**Commercial** – 6 months or to the member's renewal date, whichever is longer

**J. Esophageal Squamous Cell Carcinoma** (must meet all)**:**
1. Diagnosis of esophageal squamous cell carcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is locally advanced, recurrent, or metastatic;
5. Tumor expresses PD-L1 (CPS ≥ 10);
6. Disease has progressed on or after one or more lines of systemic therapy *(see Appendix B for examples)*;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

**Approval duration:**
**Medicaid/HIM** – 6 months
**Commercial** – 6 months or to the member's renewal date, whichever is longer

**K. Cervical Cancer** (must meet all)**:**
1. Diagnosis of cervical cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is recurrent or metastatic;
5. Tumor expresses PD-L1 (CPS ≥ 1);
6. Disease has progressed on or after ≥ 1 line of systemic therapy *(see Appendix B for examples)*;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

**Approval duration:**
**Medicaid/HIM** – 6 months
**Commercial** – 6 months or to the member's renewal date, whichever is longer

**L. Hepatocellular Carcinoma** (must meet all):
1. Diagnosis of HCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease has progressed on or after therapy with Nexavar®;
   **Prior authorization may be required for Nexavar*
5. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

**Approval duration:**
**Medicaid/HIM** – 6 months
**Commercial** – 6 months or to the member's renewal date, whichever is longer

**M. Merkel Cell Carcinoma** (must meet all)**:**
1. Diagnosis of MCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 2 years;
4. Disease is recurrent, locally advanced, or metastatic;
5. Request meets one of the following (a, b, or c):*
   a. Adults: Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Pediatrics: Dose does not exceed 2 mg/kg (up to 200 mg) every 3 weeks for a maximum of 24 months;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

**Approval duration:**

**Medicaid/HIM** – 6 months
**Commercial** – 6 months or to the member's renewal date, whichever is longer

**N. Renal Cell Carcinoma** (must meet all)**:**
1. Diagnosis of advanced RCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in combination with Inlyta®;
   **Prior authorization may be required for Inlyta.*
5. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).
   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

**Approval duration:**
**Medicaid/HIM** – 6 months
**Commercial** – 6 months or to the member's renewal date, whichever is longer

**O. Endometrial Carcinoma** (must meet all)**:**
1. Diagnosis of EC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Request meets one of the following (a or b):
   a. Prescribed in combination with Lenvima® and disease is not MSI-H or dMMR (i.e., disease is not indicative of MMR gene mutation or loss of expression);
      **Prior authorization may be required for Lenvima*
   b. Disease is MSI-H or dMMR (i.e., disease is indicative of MMR gene mutation or loss of expression);
5. Disease has progressed following prior systemic therapy (e.g., carboplatin/paclitaxel);
6. Member is not a candidate for curative surgery or radiation;
7. 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*).
   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

**Approval duration:**
**Medicaid/HIM** – 6 months
**Commercial** – 6 months or to the member's renewal date, whichever is longer

**P. NCCN Recommended Uses (off-label)** (must meet all)**:**
1. One of the following diagnoses:
   a. Keytruda is prescribed as primary or subsequent therapy:
      i. Stage III mycosis fungoides;
      ii. Stage IV Sezary syndrome;
   b. Keytruda is prescribed as subsequent therapy:
      i. Metastatic anal carcinoma;
      ii. Gestational trophoblastic neoplasia;

iii. Malignant pleural mesothelioma;
iv. Extranodal NK/T-cell lymphoma, nasal type;
v. Metastatic or unresectable thymic carcinoma;
vi. Advanced, recurrent, or metastatic PD-L1-positive (CPS ≥ 1) vulvar carcinoma;

2. Prescribed by or in consultation with an oncologist;
3. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*
**Prescribed regimen must be FDA-approved or recommended by NCCN.*

**Approval duration:**
**Medicaid/HIM** – 6 months
**Commercial** – 6 months or to the member's renewal date, whichever is longer

**Q. Other diagnoses/indications**

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

## II. Continued Therapy

**A. All Indications in Section I** (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Keytruda for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a, b, c, or d):*
   a. Melanoma: New dose does not exceed 200 mg every 3 weeks (for a maximum of 12 months if adjuvant treatment);
   b. EC: New dose does not exceed 200 mg every 3 weeks;
   c. All other FDA-approved indications: New dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   d. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

**Approval duration:**
**Medicaid/HIM** – 12 months
**Commercial** – 6 months or to the member's renewal date, whichever is longer

**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 the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**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.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

ALK: anaplastic lymphoma kinase
BCG: Bacillus Calmette-Guerin
cHL: classical Hodgkin lymphoma
CIS: carcinoma in situ
CPS: combined positive score
dMMR: mismatch repair deficient
EGFR: epidermal growth factor receptor
EC: endometrial carcinoma
FDA: Food and Drug Administration
HCC: hepatocellular carcinoma
HER2: human epidermal growth factor receptor 2
HNSCC: head and neck squamous cell carcinoma
MCC: Merkel cell carcinoma
MSI-H: microsatellite instability-high
NCCN: National Comprehensive Cancer Network
NMIBC: non-muscle invasive bladder cancer
NSCLC: non-small cell lung cancer
PD-1: programmed death protein 1
PD-L1: programmed death-ligand 1
RCC: renal cell carcinoma
ROS1: ROS proto-oncogene 1
SCLC: small cell lung cancer
TPS: tumor proportion score

*Appendix B: Therapeutic Alternatives*

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.*

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| **Section I.B: Non-Small Cell Lung Cancer**<br>Examples of drugs used in combination with Keytruda:<br>• Carboplatin, cisplatin, pemetrexed, paclitaxel<br>Examples of targeted therapies:<br>• Sensitizing EGFR mutation: erlotinib, afatinib, gefitinib, osimertinib, dacomitinib<br>• ALK mutation: crizotinib, ceritinib, alectinib, brigatinib<br>• ROS1 mutation: crizotinib, ceritinib | Varies | Varies |
| **Section I.E: Classical Hodgkin Lymphoma**<br>Examples of chemotherapy regimens:<br>• ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)<br>• Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone)<br>• BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, probarbazine, prednisone) | Varies | Varies |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| • AVD (doxorubicin, vinblastine, dacarbazine)<br>• BV (brentuximab vedotin) | | |
| **Section I.F: Primary Mediastinal Large B-Cell Lymphoma**<br>Examples of drugs used in single- or multi-drug chemotherapy regimens:<br>• Bendamustine, brentuximab vedotin, carboplatin, cisplatin, cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, gemcitabine, ibrutinib, ifosfamide, lenalidomide, mesna, mitoxantrone, methylprednisolone, oxaliplatin, prednisone, procarbazine, rituximab, vincristine, vinorelbine*<br>_____<br>**Various combinations of the listed drugs are components of the following chemotherapy regimens: CEOP, CEPP, DHAP, DHAX, EPOCH-R, ESHAP, GDP, GemOx, ICE, MINE, RCDOP, RCEOP, RCEPP, RCHOP, RGCVP* | Varies | Varies |
| **Section I.G: Urothelial Carcinoma**<br>TICE® BCG (attenuated, live culture preparation of the Bacillus of Calmette and Guerin strain of *Mycobacterium bovis* for ***intravesical*** use).<br>_____<br>References for BCG dosing, dosing in the setting of a BCG shortage, and BCG shortage status are listed below:<br>1. TICE BCG package insert: https://www.fda.gov/vaccines-blood-biologics/vaccines/tice-bcg<br>2. American Urological Association: Important message about the BCG shortage: https://www.auanet.org/about-us/bcg-shortage-info<br>3. Centers for Disease Control's current shortages page: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-regulated-products-current-shortages | Varies | Varies |
| **Section I.I and I.J: Gastric, EGJ, and Esophageal Cancer**<br>Examples of drugs used in single- or multi-drug chemotherapy regimens:*<br>• Cisplatin, carboplatin, oxaliplatin, paclitaxel, docetaxel, fluorouracil, capecitabine, irinotecan, leucovorin, epirubicin, ramucirumab (for EGJ adenocarcinoma or esophageal adenocarcinoma only)<br>_____<br>**Trastuzumab may be added to some chemotherapy regimens for HER2 overexpression.* | Varies | Varies |
| **Section I.K: Cervical Cancer**<br>Examples of drugs used in single- or multi-drug chemotherapy regimens:<br>• Cisplatin, carboplatin, paclitaxel, docetaxel, bevacizumab, topotecan, fluorouracil, gemcitabine, ifosfamide, irinotecan, topotecan, mitomycin, pemetrexed, vinorelbine | Varies | Varies |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| **Section I.L: Hepatocellular Carcinoma**<br>Nexavar (sorafenib) | 400 mg PO BID | 800 mg/day |
| **Section I.O: Endometrial Carcinoma**<br>Examples of chemotherapy regimens:*<br>• Carboplatin/paclitaxel, cisplatin/docetaxel, cisplatin/doxorubicin, carboplatin/paclitaxel/bevacizumab, carboplatin/paclitaxel/trastuzumab, ifosfamide/paclitaxel, cisplatin/ifosfamide, everolimus/letrozole, temsirolimus, Keytruda (pembrolizumab)<br>*Individual drugs used in combination regimens may also be used as monotherapy (refer to NCCN Uterine Neoplasms Guidelines)* | Varies | Varies |

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

*Appendix C: Contraindications/Boxed Warnings*
None reported

*Appendix D: Examples of Solid Tumors**
- Adrenal gland tumor
- Bladder or renal cell cancer
- Breast cancer
- Cervical, endometrial, vulvar, ovarian, fallopian tube, or primary peritoneal cancer
- Colorectal cancer
- Gallbladder cancer or intrahepatic/extrahepatic cholangiocarcinoma
- Gastric, EGJ, esophageal, or small intestinal cancer
- Pancreatic or thyroid cancer
- Penile, prostate, or testicular cancer
- Retroperitoneal adenocarcinoma
- Sarcoma (bone cancer - e.g., Ewing sarcoma; osteosarcoma; chondrosarcoma)
- Small cell lung cancer

*Examples are drawn from Keytruda pivotal trials and the NCCN compendium.*

## V. Dosage and Administration

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| Melanoma | Adults: 200 mg IV every 3 weeks<br>If adjuvant therapy, up to 12 months | 200 mg every 3 weeks |
| NSCLC, SCLC, HNSCC, cHL, PMBCL, urothelial carcinoma, MSI-H cancer, gastric cancer, esophageal squamous cell | Adults: 200 mg IV every 3 weeks up to 24 months | 200 mg every 3 weeks |

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| carcinoma, cervical cancer, HCC, MCC | | |
| cHL, PMBCL, MSI-H cancer, MCC | Pediatrics: 2 mg/kg IV every 3 weeks up to 24 months | 200 mg every 3 weeks |
| RCC | Adults: 200 mg IV every 3 weeks in combination with axitinib up to 24 months | 200 mg every 3 weeks |
| EC | Adults: 200 mg IV every 3 weeks in combination with lenvatinib | 200 mg every 3 weeks |

## VI. Product Availability

Solution, single-dose vial: 100 mg/4 mL

## VII. References

1. Keytruda Prescribing Information. Whitehouse Station, NJ: Merck and Co.; January 2020. Available at http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf. Accessed January 13, 2020
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at www.nccn.org. Accessed January 29, 2020.
3. National Comprehensive Cancer Network Guidelines. Cutaneous Melanoma Version 1.2019. Available at www.nccn.org. Accessed February 26, 2019.
4. National Comprehensive Cancer Network Guidelines. Uveal Melanoma Version 1.2018. Available at www.nccn.org. Accessed February 26, 2019.
5. National Comprehensive Cancer Network Guidelines. Non-Small Cell Lung Cancer Version 3.2019. Available at www.nccn.org. Accessed April 17, 2019.
6. National Comprehensive Cancer Network Guidelines. Small Cell Lung Cancer Version 1.2019. Available at www.nccn.org. Accessed June 25, 2019.
7. National Comprehensive Cancer Network Guidelines. Head and Neck Cancers Version 1.2019. Available at www.nccn.org. Accessed June 25, 2019.
8. National Comprehensive Cancer Network Guidelines. Hodgkin Lymphoma Version 3.2018. Available at www.nccn.org. Accessed February 26, 2019.
9. National Comprehensive Cancer Network. B-Cell Lymphomas Version 1.2019. Available at: www.nccn.org. Accessed February 26, 2019.
10. National Comprehensive Cancer Network Guidelines. Bladder Cancer Version 3.2020. Available at www.nccn.org. Accessed January 29, 2020.
11. National Comprehensive Cancer Network. Hepatobiliary Cancers Version 2.2019. Available at www.nccn.org. Accessed March 11, 2019.
12. National Comprehensive Cancer Network Guidelines. Gastric Cancer Version 2.2018. Available at www.nccn.org. Accessed February 27, 2019.
13. National Comprehensive Cancer Network Guidelines. Merkel Cell Carcinoma Version 2.2019. Available at www.nccn.org. Accessed February 27, 2019.
14. National Comprehensive Cancer Network. Cervical Cancer Version 3.2019. Available at www.nccn.org. Accessed February 27, 2019.
15. National Comprehensive Cancer Network. Kidney Cancer Version 3.2019. Available at www.nccn.org. Accessed April 20, 2019.

16. National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancers Version 2.2019. Available at www.nccn.org. Accessed August 19, 2019.
17. National Comprehensive Cancer Network. Uterine Neoplasms Version 4.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed September 23, 2019.

**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 | Description |
|---|---|
| J9271 | Injection, pembrolizumab, 1 mg |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| Policy split from CP.PHAR.182 Excellus Oncology.<br>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.<br>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.<br>Melanoma: modified max dose from 2 mg/kg to 200 mg per package insert.<br>NSCLC: added criteria for updated FDA indication (non-squamous metastatic disease).<br>HNSCC: specified that recommended NCCN off-label uses pertain to non-nasopharyngeal cancer.<br>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 |
| Criteria added for new FDA indications cervical cancer and primary mediastinal large B-cell lymphoma; urothelial carcinoma criteria updated for use in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status; added Commercial line of business; added age and specialist prescribing for all indications; applied oncology streamlining approach; added HIM-Medical Benefit line of business; reference reviewed and updated. | 07.17.18 | 08.18 |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| 4Q 2018 annual review: no significant changes; references reviewed and updated. | 07.26.18 | 11.18 |
| Added requirement for negative or unknown EGFR, ALK, ROS1, or BRAF tumor status per updated FDA indication and NCCN compendium for first-line use in metastatic nonsquamous NSCLC in combo with platinum chemotherapy and pemetrexed; streamlined criteria for subsequent use in NSCLC; references reviewed and updated. | 10.02.18 | 02.19 |
| Criteria added for new FDA indications HCC and as first-line therapy for metastatic squamous NSCLC in combination with chemotherapy; re-added criteria for PMBCL as previously approved; references reviewed and updated. | 11.27.18 | 02.19 |
| No clinical changes: off-label designation removed for MCC as it is now FDA approved. | 01.31.19 | 02.19 |
| Criteria added for new FDA indications: 1) melanoma for adjuvant treatment is incorporated by adding lymph node positive disease; complete resection is not required given additional NCCN recommended uses; age is adjusted from 2 to 18 years and older per the FDA label's indication and pediatric sections; 2) renal cell carcinoma; 3) advanced (stage III) NSCLC.<br>NSCLC: single-agent therapy for brain metastasis is added per NCCN; removal of histology requirements; mutational status requirements are limited to EGFR and ALK per the FDA label for primary therapy and to the additional NCCN directed requirement of prior ROS1 targeted therapy; subsequent therapy requirement for platinum-based chemotherapy when TPS ≥ 1% is removed since Keytruda is now FDA-approved as first-line therapy when TPS ≥ 1%.<br>HNSCC: locations as examples are incorporated into the criteria set; oxaliplatin is removed as an example as it is not listed as an NCCN recommendation for this cancer.<br>cHL and PMBCL: refractory disease is clarified by specifying at least one line of therapy; transplantation is included as a line of therapy option.<br>Urothelial carcinoma: progression as a response to platinum therapy is removed as response may include persistence or partial response.<br>MSI-H cancer: appendix updated to include solid tumors listed in the NCCN compendium and FDA label; subsequent therapy requirement is removed where recommended per NCCN; disease characteristics (e.g., metastatic) are removed to encompass NCCN recommended uses.<br>Gastric cancer: esophageal cancer and unresectable disease are added; systemic therapy examples are expanded per NCCN.<br>Cervical cancer: chemotherapy examples are expanded per NCCN. | 04.23.19 | 05.19 |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| Additional NCCN recommended uses are added as a new Section L with notation of primary versus subsequent therapy requirements. Appendix B and references reviewed and updated. | | |
| Added pediatric maximum dosing recommendations for all indications applicable to pediatrics: cHL, PMBCL, MSI-H cancer, and MCC. | 05.06.19 | |
| Criteria added for new FDA indications: 1) SCLC (previously included per NCCN as subsequent therapy; updated criteria maintains subsequent therapy but specifies prior platinum therapy; 2) HNSCC (previously post platinum therapy only; new indications include first-line combination therapy and first-line single-agent therapy, the latter if PD-L1 ≥ 1. Disease characteristics for HNSCC are updated from recurrent or metastatic, to unresectable, recurrent or metastatic; 3) dosing for all indications is limited to 24 months per the PI with the exception of melanoma and off-label uses in section I.N; 4) dosing for adjuvant melanoma therapy is limited to 12 months per the PI; 5) boilerplate language is added to all dosing sections: "Prescribed regimen must be FDA-approved or recommended by NCCN"; references reviewed and updated. | 07.09.19 | 08.19 |
| 4Q 2019 annual review: criteria added for new FDA indication for esophageal squamous cell carcinoma; criteria added for new FDA indication in endometrial carcinoma; added chondrosarcomas as another example of an NCCN-supported MSI-H/dMMR tumor type in *Appendix D*; references reviewed and updated. | 10.15.19 | 11.19 |
| Criteria added for new FDA indication: NMIBC-CIS; urologist added for UC; HIM line of business added; removed 50 mg powder single-dose vial formulation; references reviewed and updated. | 02.11.20 | 05.20 |

**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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

**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.