Clinical Policy: Pembrolizumab (Keytruda)

Reference Number: LA.PHAR.322
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Line of Business: Medicaid

Coding Implications
Revision Log

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

****Please note: This policy is for medical benefit****

Description

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

FDA Approved Indication(s)

Indication	Adults	Pediatrics
Melanoma	X	X
Non-small cell lung cancer	X	
Malignant pleural mesothelioma (MPM)	X	
Head and neck squamous cell carcinoma (HNSCC)	X	
Classical Hodgkin lymphoma	X	X
Primary mediastinal large B-cell lymphoma	X	X
Urothelial carcinoma	X	
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancer *(First-line treatment for colorectal cancer limited to adults.)*	X	X
Gastric cancer	X	
Esophageal cancer	X	
Cervical cancer	X	
Hepatocellular carcinoma	X	
Biliary tract cancer	X	
Merkel cell carcinoma	X	X
Renal cell carcinoma	X	
Endometrial carcinoma	X	
Tumor mutational burden-high (TMB-H) cancer	X	X *(excludes CNS tumor)*
Cutaneous squamous cell carcinoma	X	
Triple-negative breast cancer (TNBC)	X	
Off-label uses		
Mycosis fungoides	X	
Sezary syndrome	X	
Anal carcinoma	X	
Gestational trophoblastic neoplasia	X	
Extranodal NK/T-cell lymphoma	X	
Vulvar carcinoma	X	
Adrenocortical carcinoma	X	

Indication	Adults	Pediatrics
Alveolar soft part sarcoma	X	
Thymic carcinoma	X	
Anaplastic large cell lymphoma	X	
Small cell lung cancer	X	
Kaposi sarcoma	X	
Glioma		X

**If a solid tumor is characterized as MSI-H/dMMR or TMB-H, see criteria at Sections I.G or I.N respectively*

Keytruda is indicated:

- **Melanoma**
  - For the treatment of patients with unresectable or metastatic melanoma.
  - For the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma 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 paclitaxel protein-bound, 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.
  - For the treatment of patients with resectable (tumors ≥ 4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
  - As a single agent for the adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC.
- **Malignant pleural mesothelioma (MPM)**
  - In combination with pemetrexed and platinum chemotherapy, as first-line treatment of adult patients with unresectable advanced or metastatic MPM.
- **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 patients with relapsed or refractory cHL.
  - For the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more 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.
  - Limitations of use: Keytruda is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.
- **Urothelial carcinoma**
  - In combination with enfortumab vedotin for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma.
  - As a single agent for the treatment of patients with locally advanced or metastatic urothelial carcinoma:
    - who are not eligible for any platinum-containing chemotherapy, or
    - who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
  - As a single agent 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 (MSI-H) or mismatch repair deficient (dMMR) cancer**
  - For the treatment of adult and pediatric patients with unresectable or metastatic, MSI-H or dMMR solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
- **Microsatellite instability-high or mismatch repair deficient colorectal cancer (CRC)**
  - For the treatment of patients with unresectable or metastatic MSI-H or dMMR CRC as determined by an FDA-approved test.
- **Gastric cancer**
  - In combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS $\geq$ 1) as determined by an FDA-approved test.
  - In combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma.
- **Esophageal cancer**
  - For the treatment of patients with locally advanced or metastatic esophageal or GEJ (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
    - In combination with platinum- and fluoropyrimidine-based chemotherapy, or

    - As a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥ 10) as determined by an FDA approved test.
- **Cervical cancer**
    - In combination with chemoradiotherapy (CRT) for the treatment of patients with FIGO 2014 Stage III-IVA cervical cancer.
    - In combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.
    - As a single agent 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 secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen.
- **Biliary tract cancer (BTC)**
    - In combination with gemcitabine and cisplatin for the treatment of patients with locally advanced unresectable or metastatic BTC.
- **Merkel cell carcinoma (MCC)**
    - For the treatment of adult and pediatric patients with recurrent locally advanced or metastatic MCC.
- **Renal cell carcinoma (RCC)**
    - In combination with axitinib, for the first-line treatment of adult patients with advanced RCC.
    - In combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC.
    - For the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions.
- **Endometrial carcinoma**
    - In combination with carboplatin and paclitaxel, followed by Keytruda as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma.
    - In combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) or not MSI-H as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.
    - As a single agent for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.
- **Tumor mutational burden-high (TMB-H) cancer**
    - For the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.*

  - Limitations of use: The safety and effectiveness of Keytruda in pediatric patients with TMB-H central nervous system cancers have not been established.
- **Cutaneous squamous cell carcinoma (cSCC)**
  - For the treatment of patients with recurrent or metastatic cSCC or locally advanced cSCC that is not curable by surgery or radiation.
- **Triple-negative breast cancer (TNBC)**
  - For the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
  - In combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥ 10) as determined by an FDA approved test.
- **Adult cHL and adult PMBCL**
  - For use at an additional recommended dosage of 400 mg every 6 weeks for cHL and PMBCL in adults.**

** 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.*
*** This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this dosing 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 Louisiana HealthCare Connections® 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 ≥ 12 years;
4. Disease is Stage IIB, IIC, III, recurrent, unresectable, or metastatic;
5. Prescribed as one of the following (a, b, or c):
   a. A single agent;
   b. In combination with Lenvima® or Yervoy®;
   c. In combination with Mekinist® and Trafinlar® for disease with BRAF V600 activating mutation;
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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: 6 months

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. One of the following (a or b):
   a. Disease is resectable or resected;
   b. Disease is recurrent, advanced, or metastatic, and request meets one of the following (i, ii, iii, iv, v, or vi):
      i. Disease mutation status is negative for actionable biomarkers (EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 [HER2]);
      ii. Disease mutation status is positive for EGFR S768I, L861Q, and/or G719X, and member has received prior afatinib, osimertinib, erlotinib, gefitinib, or dacomitinib;*

iii. Disease mutation status is positive for EGFR exon 19 deletion or L858R, and member has received prior erlotinib ± (ramucirumab or bevacizumab), afatinib, gefitinib, osimertinib, or dacomitinib;*
iv. Disease mutation status is positive for ROS1 rearrangement, and member has received prior crizotinib, entrectinib, or ceritinib;*
v. Disease mutation status is positive for ALK rearrangement, and member has received prior crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib;*
vi. Disease mutation status is positive for EGFR exon 20, KRAS G12C, NRTK1/2/3, BRAF V600E, MET exon 14 skipping, RET rearrangement, or ERBB2 (HER2);

**Prior authorization may be required*

5. Keytruda is prescribed in one of the following ways (a, b, c, d, or e):
   a. For PD-L1 positive disease (TPS ≥ 1%);
   b. In combination with a chemotherapy regimen *(see Appendix B)*;
   c. In combination with a chemotherapy regimen *(see Appendix B)* as neoadjuvant treatment, followed by single-agent adjuvant treatment after surgery for patients with resectable (tumors ≥ 4 cm or node positive) disease;
   d. As single-agent continuation maintenance therapy if previously given first line as part of a chemotherapy regimen;
   e. As single-agent adjuvant treatment following resection and platinum-based chemotherapy (e.g., cisplatin, carboplatin) for adult patients with stage IB (T2a ≥ 4 cm), II, or IIIA disease;
6. Member does not have contraindications to PD-1/PD-L1 inhibitor therapy (e.g., Opdivo®, Yervoy, Tecentriq®, Imfinzi®) (*see Appendix F*);
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 weeks for a maximum duration of one of the following (i, ii, or iii):
      i. 24 months;
      ii. 12 months if adjuvant treatment;
      iii. 12 weeks if neoadjuvant treatment, followed by 39 weeks of 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: 6 months

C. Malignant Pleural Mesothelioma (must meet all)**:**

1. Diagnosis of MPM;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is unresectable, advanced, or metastatic;
5. Keytruda is prescribed in combination with pemetrexed and platinum-containing chemotherapy;
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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: 6 months

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. Keytruda is prescribed in one of the following ways (a, b, or c):
   a. In combination with platinum-containing chemotherapy and either FU, docetaxel, or gemcitabine;
   b. As a first-line single agent and the tumor expresses PD-L1 with a CPS of ≥ 1;
   c. As a single agent for disease that has progressed on or after platinum-containing chemotherapy (e.g., cisplatin, carboplatin);
6. For nasopharyngeal carcinoma, failure of Loqtorzi® at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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: 6 months

E. Classical Hodgkin Lymphoma (must meet all)**:**

1. Diagnosis of cHL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 6 months;
4. Keytruda is prescribed as single-agent therapy (*adults or pediatrics*) or in combination with GVD (gemcitabine, vinorelbine, liposomal doxorubicin) or ICE (ifosfamide, carboplatin, etoposide) (*adults only*) in one of the following ways (a, b, c, or d):
   a. For palliative therapy;
   b. For disease that is refractory to ≥ 1 line of systemic therapy (*see Appendix B*);
   c. Age ≥ 18 years: For disease that has relapsed after ≥ 1 line of systemic therapy (*see Appendix B*);
   d. Age ≥ 6 months to < 18 years: For disease that has relapsed after ≥ 2 lines of systemic therapy (*see Appendix B*);
5. Request meets one of the following (a, b, or c):*
   a. Adults: Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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: 6 months

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 ≥ 6 months;
4. Disease is refractory to or has relapsed after ≥ 1 line of systemic therapy *(see Appendix B)*;
5. Prescribed in one of the following ways (a or b):
   a. As a single agent;
   b. For age ≥ 6 months to < 18 years only, in combination with Adcetris®;
6. Request meets one of the following (a, b, or c):*
   a. Adults: Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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: 6 months

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. Keytruda is prescribed in one of the following ways (a, b, or c):
   a. In combination with Padcev® for locally advanced or metastatic disease;
   b. As a single agent for locally advanced or metastatic disease, and member is ineligible for or has previously received platinum-containing chemotherapy (e.g., cisplatin, carboplatin) or previously received other chemotherapy;
   c. As a single agent for the treatment of BCG-unresponsive, high-risk, NMIBC with CIS, and member is ineligible for or has elected not to undergo cystectomy (*see Appendix D for BCG shortage information*);
5. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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: 6 months

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 E for examples of MSI-H solid tumors)*;

2. Prescribed by or in consultation with an oncologist;
3. Member meets one of the following (a or b):
   a. Age ≥ 6 months to < 18 years and request is not for first-line therapy;
   b. Age ≥ 18 years;
4. Keytruda is prescribed in one of the following ways (a or b):
   a. As first-line or subsequent therapy for ampullary adenocarcinoma, CRC, gallbladder cancer, gastric cancer, GEJ cancer, intrahepatic/extrahepatic cholangiocarcinoma, non-nasopharyngeal head, and neck cancer, occult primary tumor, pancreatic adenocarcinoma, or small bowel adenocarcinoma;
   b. As subsequent therapy for other solid tumors;
5. Prescribed in one of the following ways (a or b):
   a. As a single agent;
   b. For gastric or GEJ cancers: as a single agent or in combination with platinum- and fluoropyrimidine-based chemotherapy;
6. Request meets one of the following (a, b, or c):*
   a. Adults: Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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: 6 months

I. Gastric Cancer, Esophageal Cancer, or Gastroesophageal Junction Cancer (must meet all)**:**

1. Diagnosis of gastric cancer, esophageal cancer, or GEJ cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. One of the following (a or b):
   a. Disease is unresectable, locally advanced, recurrent, or metastatic;
   b. Member is planned for esophagectomy;
5. Keytruda is prescribed in one of the following ways (a, b, or c):
   a. In combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, and both (i and ii):
      i. HER2-positive gastric or GEJ adenocarcinoma;
      ii. Tumor expresses PD-L1 (CPS ≥ 1);
   b. In combination with platinum- and fluoropyrimidine-based chemotherapy, and either (i or ii):
      i. HER2-negative gastric or GEJ adenocarcinoma;
      ii. Esophageal carcinoma or GEJ squamous cell carcinoma;
   c. As a single agent after one or more prior lines of systemic therapy for members with tumors of squamous cell GEJ that express PD-L1 (CPS ≥ 10) *(see Appendix B)*;
6. Request meets one of the following (a or b):*

a. Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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: 6 months

J. Cervical Cancer (must meet all)**:**

1. Diagnosis of cervical cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in one of the following ways (a, b, or c):
   a. As a single agent, and all of the following (i, ii, and iii):
      i. Tumor expresses PD-L1 (CPS ≥ 1);
      ii. Disease is recurrent or metastatic;
      iii. Disease has progressed on or after ≥ 1 line of systemic therapy *(see Appendix B)*;
   b. In combination with chemotherapy (e.g., paclitaxel/cisplatin, paclitaxel/carboplatin) with or without bevacizumab, and both (i and ii):
      i. Tumor expresses PD-L1 (CPS ≥ 1);
      ii. Disease is persistent, recurrent, or metastatic;
   c. In combination with CRT, and (i):
      i. Disease is FIGO 2014 Stage III-IVA (*see Appendix F*);
5. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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: 6 months

K. Hepatocellular Carcinoma (must meet all):

1. Diagnosis of HCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. One of the following (a or b):
   a. Disease progressed on or after therapy with Nexavar®, Lenvima, Stivarga®, or Cabometyx®, and (i):
      i. Member has not previously been treated with immune checkpoint inhibitor therapy (PD-L1/PD-1, e.g., Tecentriq, Opdivo);

      **Prior authorization may be required for Nexavar, Lenvima and Stivarga*
   b. Prescribed as first line treatment;
5. Prescribed as a single agent;
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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: 6 months

L. Biliary Tract Cancer (must meet all):

1. Diagnosis of BTC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is locally advanced unresectable, or resected gross residual (R2) disease or metastatic;
5. Prescribed in combination with gemcitabine and cisplatin;
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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: 6 months

M. Merkel Cell Carcinoma (must meet all)**:**

1. Diagnosis of MCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 6 months;
4. Disease is recurrent, locally advanced, or metastatic;
5. Prescribed as a single agent;
6. Request meets one of the following (a, b, or c):*
   a. Adults: Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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: 6 months

N. Renal Cell Carcinoma (must meet all)**:**

1. Diagnosis of RCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Keytruda is prescribed in one of the following ways (a, b, or c):
   a. In combination with Inlyta® or Lenvima*, and disease is advanced (i.e., relapsed or stage IV);
      **Prior authorization may be required for Inlyta and Lenvima.*
   b. As single-agent adjuvant treatment, and member is at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions;

c. As a single agent for relapsed or stage IV disease with non-clear cell histology (off-label);

5. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 weeks for a maximum of 24 months (combination therapy) or 12 months (monotherapy);
   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: 6 months

O. Endometrial Carcinoma (must meet all)**:**

1. Diagnosis of endometrial carcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in one of the following (a or b):
   a. In combination with Lenvima* and both of the following (i and ii):
      **Prior authorization may be required for Lenvima*
      i. Disease is pMMR or not MSI-H;
         **See criteria set I.G. for MSI-H/dMMR endometrial carcinoma*
      ii. Progressed following prior systemic therapy (e.g., carboplatin/paclitaxel);
   b. In combination with carboplatin and paclitaxel and continued as a single agent for maintenance therapy for advanced, recurrent, or Stage III-IV disease;
5. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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: 6 months

P. Tumor Mutational Burden-High Cancer (must meet all)**:**

1. Diagnosis of a solid tumor classified as TMB-H (i.e., ≥ 10 mutations/megabase [mut/Mb]) (*see Appendix E for examples of TMB-H solid tumors*);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 6 months;
4. Disease is unresectable or metastatic;
5. One of the following (a or b):
   a. Disease has progressed following prior treatment;
   b. Prescribed as a first-line therapy for ampullary adenocarcinoma or pancreatic adenocarcinoma;
6. Prescribed as a single agent;
7. Request meets one of the following (a, b, or c):*
   a. Adults: Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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: 6 months

Q. Cutaneous Squamous Cell Carcinoma (must meet all)**:**

1. Diagnosis of cSCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Member is not a candidate for curative surgery or radiation;
5. Prescribed as a single agent;
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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: 6 months

R. Triple Negative Breast Cancer (must meet all)**:**

1. Diagnosis of TNBC (i.e., estrogen receptor/progesterone receptor [ER/PR] negative and human epidermal growth factor receptor 2 [HER2]-negative);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. One of the following (a or b):
   a. Disease is high-risk early-stage (*see Appendix F*), and:
      i. Prescribed in combination with chemotherapy (e.g., carboplatin, paclitaxel, doxorubicin, cyclophosphamide) as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery;
   b. Disease is locally recurrent unresectable or metastatic, and both of the following (i and ii):
      i. Tumor expresses PD-L1 (CPS ≥ 10);
      ii. Prescribed in combination with chemotherapy (e.g., paclitaxel, paclitaxel protein-bound, gemcitabine and carboplatin);
5. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 weeks for a maximum of (i or ii):
      i. High-risk, early-stage TNBC: 24 weeks as neoadjuvant therapy and 27 weeks as adjuvant therapy;
      ii. Locally recurrent unresectable or metastatic TNBC: 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: 6 months

S. Glioma (off-label) (must meet all):

1. Diagnosis of hypermutant tumor diffuse high-grade glioma;

2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 6 months and < 18 years;
4. 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: 6 months

T. NCCN Recommended Uses (off-label) (must meet all)**:**

1. Diagnosis of one of the following (a, b, or c):
   a. Keytruda is prescribed as first-line or subsequent therapy:
      i. Stage IB or III mycosis fungoides;
      ii. Stage IV Sezary syndrome;
      iii. Unresectable or metastatic adrenocortical carcinoma;
      iv. Alveolar soft part sarcoma;
      v. Angiosarcoma;
      vi. Metastatic or unresectable thymic carcinoma, and prescribed as a single agent;
      vii. Metastatic anaplastic carcinoma;
      viii. Vaginal cancer;
   b. Keytruda is prescribed as single-agent subsequent therapy:
      i. Metastatic anal carcinoma, and member has not previously received Keytruda or Opdivo;
      ii. Gestational trophoblastic neoplasia;
      iii. Extranodal NK/T-cell lymphoma;
      iv. Advanced, recurrent, or metastatic PD-L1-positive (CPS ≥ 1) vulvar carcinoma;
      v. Relapsed or refractory cutaneous anaplastic large cell lymphoma;
      vi. Relapsed or primary progressive small cell lung cancer;
      vii. Endemic or classic Kaposi sarcoma;
      viii. Soft tissue sarcoma subtypes: Myxofibrosarcoma, undifferentiated pleomorphic sarcoma (UPS), dedifferentiated liposarcoma, cutaneous angiosarcoma, and undifferentiated sarcomas;
   c. Keytruda is prescribed in combination with cyclophosphamide and bevacizumab for platinum-resistant persistent ovarian cancer, fallopian tube cancer, primary peritoneal cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. 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: 6 months

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy LA.PMN.53

II. Continued Therapy

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

1. Currently receiving medication via Louisiana Healthcare Connections 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. Member has NOT received the maximum duration of therapy as described below (a, b, c, or d):
   a. Adjuvant melanoma treatment or RCC monotherapy: up to 12 months;
   b. For high-risk, early stage TNBC: up to 24 weeks if neoadjuvant treatment, followed by 27 weeks as adjuvant treatment;
   c. NSCLC, one of the following (i, ii, or iii):
      i. 24 months;
      ii. 12 months if adjuvant treatment;
      iii. 12 weeks if neoadjuvant, followed by 39 weeks of adjuvant treatment;
   d. All other FDA-approved indications: up to 24 months;
4. If request is for a dose increase, request meets one of the following (a, b, or c):*
   a. Adults (i or ii):
      i. New dose does not exceed 200 mg every 3 weeks;
      ii. New dose does not exceed 400 mg every 6 weeks;
   b. Pediatrics: New dose does not exceed 2 mg/kg up to 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*).

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

Approval duration: 12 months

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy LA.PMN.53

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 LA.PMN.53

B. Pediatric patients with MSI-H or TMB-H central nervous cancers.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALK: anaplastic lymphoma kinase
BCG: Bacillus Calmette-Guerin
BTC: biliary tract cancer
cHL: classical Hodgkin lymphoma
CIS: carcinoma in situ
CNS: central nervous system
CPS: combined positive score
CRC: colorectal cancer
CRT: chemoradiotherapy
cSCC: cutaneous squamous cell carcinoma
dMMR: mismatch repair deficient
EGFR: epidermal growth factor receptor
FDA: Food and Drug Administration
GEJ: gastroesophageal junction
HCC: hepatocellular carcinoma
HER2: human epidermal growth factor receptor 2
HNSCC: head and neck squamous cell carcinoma
MCC: Merkel cell carcinoma
MPM: malignant pleural mesothelioma
MSI-H: microsatellite instability-high
mut/Mb: mutations/megabase
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
PMBCL: primary mediastinal large B-cell lymphoma
pMMR: mismatch repair proficient
RCC: renal cell carcinoma
ROS1: ROS proto-oncogene 1
TMB-H: tumor mutational burden-high
TNBC: triple-negative breast 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 and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Section I.B: Non-Small Cell Lung Cancer Examples of drugs used in combination with Keytruda: • Carboplatin, cisplatin, pemetrexed, paclitaxel Examples of targeted therapies: • EGFR S768I, L861Q, and/or G719X targeted therapies: afatinib, osimertinib, erlotinib, gefitinib, dacomitinib • EGFR exon 19 deletion or L858R targeted therapies: erlotinib ± (ramucirumab or bevacizumab), afatinib, gefitinib, osimertinib, dacomitinib • ROS1 targeted therapies: crizotinib, entrectinib, ceritinib • ALK rearrangement targeted therapies: crizotinib, ceritinib, alectinib, brigatinib, lorlatinib	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Section I.D: Head and Neck Squamous Cell Carcinoma Nasopharyngeal carcinoma (NPC) • Loqtorzi (toripalimab-tpzi)	First-line treatment for NPC: 240 mg IV every three weeks up to 24 months in combination with cisplatin and gemcitabine Previously treated, unresectable or metastatic NPC 3 mg/kg IV every two weeks	First-line treatment for NPC: 240 mg/3 weeks Previously treated, unresectable or metastatic NPC 3 mg/kg every two weeks
Section I.E: Classical Hodgkin Lymphoma Adults: Examples of chemotherapy regimens: • ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) • Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone) • BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, probarbazine, prednisone) • Brentuximab vedotin + AVD (doxorubicin, vinblastine, dacarbazine) Pediatrics: Examples of chemotherapy regimens • AVPC (doxorubicin, vincristine, prednisone, cyclophosphamide) • ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide) • Brentuximab vedotin + bendamustine • ICE (ifosfamide, carboplatin, etoposide)	Varies	Varies
Section I.F: Primary Mediastinal Large B-Cell Lymphoma Examples of drugs used in single- or multi-drug chemotherapy regimens: • Bendamustine, brentuximab vedotin, carboplatin, cisplatin, cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, gemcitabine, ibrutinib, ifosfamide, lenalidomide,	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
mesna, mitoxantrone, methylprednisolone, oxaliplatin, prednisone, procarbazine, rituximab, vincristine, vinorelbine* **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*		
Section I.G: Urothelial Carcinoma TICE® BCG (attenuated, live culture preparation of the Bacillus of Calmette and Guerin strain of *Mycobacterium bovis* for ***intravesical*** use). References for BCG dosing, dosing in the setting of a BCG shortage, and BCG shortage status are listed below and at Appendix D: 1. TICE BCG package insert: https://www.fda.gov/vaccines-blood-biologics/vaccines/tice-bcg 2. American Urological Association: Important message about the BCG shortage: https://www.auanet.org/about-us/bcg-shortage-info 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: Gastric, EGJ, and Esophageal Cancer Examples of drugs used in single- or multi-drug chemotherapy regimens:* • Cisplatin, carboplatin, oxaliplatin, paclitaxel, docetaxel, fluorouracil, capecitabine, irinotecan, leucovorin, epirubicin, ramucirumab (for EGJ adenocarcinoma or esophageal adenocarcinoma only) **Trastuzumab may be added to some chemotherapy regimens for HER2 overexpression.*	Varies	Varies
Section I.J: Cervical Cancer Examples of drugs used in single- or multi-drug chemotherapy regimens: • Cisplatin, carboplatin, paclitaxel, docetaxel, bevacizumab, topotecan, fluorouracil, gemcitabine, ifosfamide, irinotecan, topotecan, mitomycin, pemetrexed, vinorelbine Examples of CRT regimens: • Cisplatin plus external beam radiation therapy (EBRT), followed by brachytherapy (BT)	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Section I.K: Hepatocellular Carcinoma Nexavar (sorafenib)	400 mg PO BID	800 mg/day
Section I.K: Hepatocellular Carcinoma Lenvima (lenvatinib)	12 mg PO QD (patients ≥ 60 kg) or 8 mg PO QD (patients < 60 kg)	12 mg/day
Section I.K: Hepatocellular Carcinoma Stivarga (regorafenib)	160 mg PO QD for the first 21 days of each 28-day cycle	160 mg/day on days 1 to 21, every 28 days
Section I.K: Hepatocellular Carcinoma Cabometyx (cabozantinib)	60 mg PO QD	60 mg/day
Section I.O: Endometrial Carcinoma Examples of chemotherapy regimens:* • Carboplatin/paclitaxel, cisplatin/docetaxel, cisplatin/doxorubicin, carboplatin/paclitaxel/bevacizumab, carboplatin/paclitaxel/trastuzumab, ifosfamide/paclitaxel, cisplatin/ifosfamide, everolimus/letrozole, temsirolimus, Keytruda (pembrolizumab) **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: Keytruda Therapy for Urinary Bladder CIS in the Event of a BCG Shortage
- National Comprehensive Cancer Network (NCCN) information and recommendations:
  - Standard urinary bladder CIS therapy includes lesion resection followed by intravesical BCG.
  - The NCCN advises that in the event of a BCG shortage, BCG should be prioritized for induction of high-risk patients (e.g., high-grade T1 and CIS) and that, if feasible, the dose of BCG may be split (1/3 or 1/2 dose) so that multiple patients may be treated with a single vial in the event of a shortage.
  - If BCG is unavailable, the NCCN recommends the following alternatives:
    - Intravesical chemotherapy agents as first-line and subsequent therapy (e.g., gemcitabine, mitomycin, epirubicin, valrubicin, docetaxel, sequential gemcitabine/docetaxel, gemcitabine/mitomycin);
    - Initial radical cystectomy if patient is a surgical candidate.

  - The NCCN recommendations do not include off-label use of Keytruda as first-line or subsequent therapy in the absence of BCG failure.
- In its BCG June 2020 supply update sent to providers, Merck confirms a path forward to expand BCG manufacturing but cautions that the expansion could take years to fully realize. Merck directs providers to their wholesalers and distributors for supply questions and also provides its National Service Center number (800-672-6372) for additional information.

1. *National Comprehensive Cancer Network Guidelines. Bladder Cancer Version 5.2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed July 10, 2020.*
2. *Merck Supply Update: TICE BCG LIVE (for intravesical use). June 2020.*

Appendix E: Examples of Solid Tumors per Pivotal Trials by "N" (descending)

MSI-H Solid Tumors	TMB-H Solid Tumors
CRC	Small cell lung cancer
Endometrial cancer	Cervical cancer
Biliary cancer	Endometrial cancer
Gastric or GE junction cancer	Anal cancer
Pancreatic cancer	Vulvar cancer
Small intestinal cancer	Neuroendocrine cancer
Breast cancer	Salivary cancer
Prostate cancer	Thyroid cancer
Bladder cancer	Mesothelioma cancer
Esophageal cancer	*Additional examples – NCCN compendium*: Adrenal tumor, ampullary adenocarcinoma, breast cancer, ovarian / fallopian tube / primary peritoneal cancer, chondroma, chondrosarcoma, head and neck cancer, Ewing sarcoma, nasopharynx cancer, occult primary carcinoma, osteosarcoma, pancreatic cancer, prostate cancer, testicular cancer, soft tissue sarcoma, uterine sarcoma, vaginal cancer
Sarcoma	
Thyroid cancer	
Retroperitoneal adenocarcinoma	
Small cell lung cancer	
Renal cell cancer	
Additional examples – NCCN compendium: Adrenal tumor, ampullary adenocarcinoma, cervical / vulvar / ovarian / fallopian tube / primary peritoneal cancer, chondrosarcoma, chondroma, Ewing sarcoma, head and neck cancer, hepatocellular carcinoma, neuroendocrine cancer, occult primary carcinoma, osteosarcoma, penile cancer, small bowel adenocarcinoma, testicular cancer, vaginal cancer	

Appendix F: General Information

- High-risk early-stage TNBC was defined as tumor size > 1 cm but ≤ 2 cm in diameter with nodal involvement or tumor size > 2 cm in diameter regardless of nodal involvement in the pivotal KEYNOTE-522 study.
- Although Keytruda's approval for small cell lung cancer was withdrawn due to lack improvement in overall survival in phase 3 randomized trial data, the NCCN continues to

recommend this use, stating that "pembrolizumab [is] just as effective as, and sometimes better than, the other subsequent therapy options."

- Per NCCN, contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents, or presence of an oncogene (i.e., EGFR exon 19 deletion or exon 21 L858R, ALK rearrangements), which has been shown to be associated with less benefit.
- FIGO 2014 Stage III-IVA cervical cancer is defined as tumor involvement of the lower vagina with or without extension onto pelvic sidewall or hydronephrosis/non-functioning kidney or has spread to adjacent pelvic organs.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Pediatrics		
cHL, PMBCL, MSI-H or dMMR cancer, MCC, TMB-H cancer	2 mg/kg IV every 3 weeks up to 24 months	200 mg every 3 weeks
Melanoma	2 mg/kg IV every 3 weeks up to 12 months	200 mg every 3 weeks
Adults		
Melanoma	200 mg IV every 3 weeks OR 400 mg every 6 weeks If adjuvant therapy up to 12 months	200 mg every 3 weeks OR 400 mg every 6 weeks
NSCLC	200 mg IV every 3 weeks OR 400 mg every 6 weeks up to 24 months* OR up to 12 months for adjuvant treatment** OR 12 weeks for neoadjuvant treatment*** followed by adjuvant treatment for 39 weeks** _____ **As single-agent therapy or in combination with chemotherapy* ***As single-agent therapy* **** In combination with chemotherapy*	200 mg every 3 weeks OR 400 mg every 6 weeks
HNSCC, cHL, PMBCL, urothelial carcinoma, MSI-H or dMMR cancer	200 mg IV every 3 weeks OR 400 mg	200 mg every 3 weeks OR 400 mg every 6 weeks

Indication	Dosing Regimen	Maximum Dose
(including endometrial carcinoma), gastric cancer, esophageal cancer, cervical cancer, HCC, BTC, MCC, TMB-H cancer, cSCC	every 6 weeks up to 24 months* _____ **Esophageal cancer, gastric cancer, or HNSCC: as single-agent therapy or in combination with chemotherapy.* *For cervical cancer: as single-agent therapy or in combination with chemotherapy or CRT* *For urothelial carcinoma: as single-agent therapy or in combination with Padcev.* *For BTC: in combination with chemotherapy*	
Indication	**Dosing Regimen**	**Maximum Dose**
Pediatrics		
cHL, PMBCL, MSI-H or dMMR cancer, MCC, TMB-H cancer	2 mg/kg IV every 3 weeks up to 24 months	200 mg every 3 weeks
Melanoma	2 mg/kg IV every 3 weeks up to 12 months	200 mg every 3 weeks
Adults		
Melanoma	200 mg IV every 3 weeks OR 400 mg every 6 weeks If adjuvant therapy up to 12 months	200 mg every 3 weeks OR 400 mg every 6 weeks
NSCLC	200 mg IV every 3 weeks OR 400 mg every 6 weeks up to 24 months* OR up to 12 months for adjuvant treatment** OR 12 weeks for neoadjuvant treatment*** followed by adjuvant treatment for 39 weeks** **As single-agent therapy or in combination with chemotherapy* ***As single-agent therapy* **** In combination with chemotherapy*	200 mg every 3 weeks OR 400 mg every 6 weeks

Indication	Dosing Regimen	Maximum Dose
HNSCC, MPM, cHL, PMBCL, urothelial carcinoma, MSI-H or dMMR cancer (including endometrial carcinoma), gastric cancer, esophageal cancer, cervical cancer, HCC, BTC, MCC, TMB-H cancer, cSCC	200 mg IV every 3 weeks OR 400 mg every 6 weeks up to 24 months* **Esophageal cancer, gastric cancer, or HNSCC: as single-agent therapy or in combination with chemotherapy* *For cervical cancer: as single-agent therapy or in combination with chemotherapy or CRT* *For urothelial carcinoma: as single-agent therapy or in combination with Padcev.* *For BTC, MPM: in combination with chemotherapy*	200 mg every 3 weeks OR 400 mg every 6 weeks
RCC (combination therapy)	200 mg IV every 3 weeks OR 400 mg every 6 weeks in combination with axitinib or lenvatinib up to 24 months	200 mg every 3 weeks OR 400 mg every 6 weeks
RCC (monotherapy)	200 mg IV every 3 weeks OR 400 mg every 6 weeks for up to 12 months	200 mg every 3 weeks OR 400 mg every 6 weeks
Endometrial carcinoma (combination therapy)	200 mg IV every 3 weeks OR 400 mg every 6 weeks prior to carboplatin and paclitaxel when given on the same day or in combination with lenvatinib, up to 24 months	200 mg every 3 weeks OR 400 mg every 6 weeks
TNBC	200 mg IV every 3 weeks OR 400 mg every 6 weeks* for the following durations: • High-risk early-stage TNBC – neoadjuvant: 24 weeks	200 mg every 3 weeks OR 400 mg every 6 weeks

Indication	Dosing Regimen	Maximum Dose
	• High-risk early-stage TNBC – adjuvant: 27 weeks • Locally recurrent unresectable metastatic TNBC: 24 months **In combination with chemotherapy for high-risk early-stage TNBC when used as neoadjuvant treatment and for locally recurrent unresectable or metastatic TNBC.*	

VI. Product Availability

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

VII. References

1. Keytruda Prescribing Information. Whitehouse Station, NJ: Merck and Co.; March 2025. Available at http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf. Accessed March 26, 2025.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at https://www.nccn.org/professionals/drug_compendium/content/. Accessed March 27, 2025.
3. Salem ME, Puccini A, Grothey A, et al. Landscape of tumor mutation load, mismatch repair deficiency, and PD-L1 expression in a large patient cohort of gastrointestinal cancers. Molecular cancer research: MCR. 2018;16(5):805-812. https://pubmed.ncbi.nlm.nih.gov/29523759/.

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	LDH Approval Date
Converted corporate to local policy	01.21	04.28.21
FDA cHL label updated from relapsed disease after 3 lines of therapy to after 1 line of therapy (adults) or 2 lines of therapy (pediatrics); new NCCN pediatric cHL guideline added to reference section; new FDAapproved TNBC indication added. Ad hoc change: for HCC, Lenvima added as a prior therapy option per NCCN.	02.22	05.05.22

Reviews, Revisions, and Approvals	Date	LDH Approval Date
Criteria added for newly approved indications of 1) esophageal/GEJ junction carcinoma, 2) combo use for 1st line gastric or GEJ adenocarcinoma, 3) locally advanced cutaneous squamous cell carcinoma, and 4) high-risk early-stage TNBC; removed SCLC indication and criteria; updated FDA labeled indication for endometrial carcinoma to remove accelerated approval language and modified criteria to be consistent with FDA language; updated FDA labeled indication language for MSI-H/dMMR cancer; Criteria added for new FDA approved indication: RCC in combination with Lenvatinib; Updated FDA Approved Indication(s) section to reflect revised indication for metastatic urothelial carcinoma (removal of use in patients "who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test") - no change to criteria required. Criteria added for new FDA approved indication: cervical cancer in combination with chemotherapy with or without bevacizumab. Criteria added for new FDA approved indication: adjuvant treatment of RCC. For melanoma criteria added per updated prescribing information for pediatric extension in stage III disease and new indications for both adults and pediatrics for stage IIB and IIC; for RCC clarified maximum dosing for initial and continued approvals to distinguish length of therapy for 12 months in monotherapy and 24 months for combination therapy.		
Removal of previously approved indication for usage as third-line monotherapy for PD-L1 positive gastric/GEJ cancer patients per updated prescribing information Updated FDA Approved Indication(s) section to include newly approved indication for use as monotherapy for MSI-H or dMMR endometrial carcinoma (no change to criteria required) and for use with gemcitabine and cisplatin for BTC; revisions per NCCN – melanoma: added requirement for use as a single agent or in combination with Lenvima or Yervoy; NSCLC: added requirement for no contraindications to PD-1/PD-L1 inhibitors, clarified criteria regarding disease mutation status (disease should be negative for actionable biomarkers and prior targeted therapy is now required only for ROS1 and EGFR S768I, L861Q, and/or G719X mutations), added pathway for use as single-agent continuation maintenance therapy if previously given first line as part of a chemotherapy regimen; HNSCC: added pathway for combination use with docetaxel or gemcitabine; cHL: added pathway for combination use with GVD in adults; cSCC, HCC, PMBCL: added requirement for use as a single agent; urothelial carcinoma: added requirement for use as a single agent for locally advanced or metastatic disease in members who are ineligible for or have previously received platinum-containing chemotherapy; MSI-H/dMMR cancers: added additional cancers for which Keytruda may be used first line (ampullary adenocarcinoma, non-nasopharyngeal head and neck cancer, pancreatic adenocarcinoma), removed requirement for oxaliplatin contraindication for small bowel adenocarcinoma, added requirement for use as a single agent; RCC: added requirement for use as a single agent for adjuvant treatment; TMB-H cancer: added pathway for use as first-line for ampullary adenocarcinoma or	11.22.23	01.23.24

Reviews, Revisions, and Approvals	Date	LDH Approval Date
pancreatic adenocarcinoma, added requirement for use as a single agent; off-label uses: added additional coverable cancers (adrenocortical carcinoma, alveolar soft part sarcoma, anaplastic large cell lymphoma, small cell lung cancer), added pathway for use as first line for thymic carcinoma, removed use for malignant pleural mesothelioma, updated mycosis fungoides to allow stage IIB, updated anal carcinoma to require no prior treatment with Keytruda or Opdivo, updated cancers where Keytruda is to be used only as subsequent therapy to require use as a single agent, updated extranodal NK/T-cell lymphoma to remove nasal type specification; revised legacy. For endometrial carcinoma for use in combination with Lenvima, revised dMMR to pMMR per updated FDA approved indication. Added criteria for newly FDA approved indication of single-agent adjuvant therapy for NSCLC, added "as determined by an FDA-approved test" for MSI-H/dMMR cancer and microsatellite instability-high or mismatch repair deficient CRC, and revised "adult indications: additional dosing regimen" to apply only to adult cHL and PMBCL per updated PI; revised NSCLC criteria to include additional requirements related to mutation status per NCCN compendium. Added additional urothelial cancer indication in combination with enfortumab vedotin for patients ineligible for cisplatin-containing chemotherapy, and updated FDA approved indication for MSI-H/dMMR solid tumors to reflect full FDA approval per PI. Template changes applied to other diagnoses/indications. Adjusted pediatric age from 2 years to 6 months per PI/KEYNOTE-051; for Melanoma added option to be prescribed in combination with Mekinist and Trafinlar for disease with BRAF V600 activating mutation per NCCN; added endemic or classic Kaposi Sarcoma for adult off-label use and hypermutant tumor diffuse high-grade glioma for pediatric off-label use per NCNN; added criterion prescribed as single agent for Merkel cell carcinoma per NCCN; for HCC, added option for Stivarga; for pediatric PMBCL added option to be prescribed in combination with Adcetris; for endometrial carcinoma added option for combination with carboplatin and paclitaxel if disease is recurrent or stage III-IV tumor; references reviewed and updated. Included Relapsed or primary progressive small cell lung cancer and Endemic or classic Kaposi Sarcoma to the NCCN off-label use single-agent therapy categories. Minor formatting changes.		
Updated FDA-approved indication section for HCC to full approval with update from those "who have previously been treated with sorafenib" to "secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen" per PI; for HCC, added option for prior use of Cabometyx and added option to be prescribed as first-line treatment per NCCN.	06.14.24	09.04.24
For cHL, added option to be prescribed with ICE and added pathway for palliative therapy (previously had after hematopoietic stem cell transplant, which falls under	10.09.24	1.27.25

Reviews, Revisions, and Approvals	Date	LDH Approval Date
palliative therapy) per NCCN; for UC, added pathway to be prescribed as single agent and member has previously received other chemotherapy (previously only allowed post-platinum chemotherapy); for HCC, removed disease is classified as Child-Pugh Class A; for BTC, added option for resected gross residual (R2) disease and removed combination with Lenvima per NCCN; for endometrial carcinoma, clarified continued as a single agent for maintenance therapy when prescribed in combination with carboplatin and paclitaxel; for NCCN recommended uses (off-label): expanded to stage IB for mycosis fungoides, for prescribed as first-line or subsequent therapy - added metastatic anaplastic carcinoma, anaplastic sarcoma, and vaginal cancer, for prescribed as single-agent subsequent therapy – added soft tissue sarcoma subtypes, added option for Keytruda to be prescribed in combination with cyclophosphamide and bevacizumab for platinum-resistant persistent ovarian cancer, fallopian tube cancer, and primary peritoneal cancer per NCCN; for continuation requests, added criterion for maximum duration of therapy (previously was included within requests for dose increase criterion); updated appendix E; references reviewed and updated. Added new FDA approved indication for endometrial cancer in combination with carboplatin and paclitaxel followed by Keytruda as a single agent per PI.		
For HNSCC, added redirection for nasopharyngeal carcinoma to Loqtorzi; updated FDA Approved Indication(s) section for first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy whose tumors express PD-L1 (CPS ≥ 1) from accelerated approval to full approval per PI; for gastric cancer, esophageal cancer, or GEJ cancer, added option to bypass disease is unresectable, locally advanced, recurrent, or metastatic if member is planned for esophagectomy per NCCN.	6.15.25	

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. LHCC 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.

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 LHCC administrative policies and procedures.

This clinical policy is effective as of the date determined by LHCC. 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. LHCC 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 LHCC has no control or right of control. Providers are not agents or employees of LHCC.

This clinical policy is the property of LHCC. 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.