Kansas City

An Independent Licensee of the Blue Cross and Blue Shield Association

Keytruda (pembrolizumab)- Medicare Advantage Only

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Last Review: 06/2024
Next Review: 06/2025

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for **Keytruda (pembrolizumab)** when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

Keytruda (pembrolizumab) may be considered **medically necessary** when all the following criteria are met:

FDA Approved Indications:
Keytruda (pembrolizumab) may be considered **medically necessary** when the following criteria are met:

FDA Approved Indications:

1. **Biliary tract cancer (BTC), locally advanced unresectable or metastatic**
    a. Treatment in combination with cisplatin and gemcitabine.
2. **Melanoma**
    a. For the treatment of patients with unresectable or metastatic melanoma.
    b. For the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma following complete resection.
3. **Non-Small Cell Lung Cancer (NSCLC)**
    a. Adjuvant treatment (as a single agent) of stage IB (T2a ≥4 cm), II, or IIIA non–small cell lung cancer (NSCLC) following resection and platinum-based chemotherapy in adults.
    b. First-line monotherapy in patients with
        i. stage III NSCLC (who are not candidates for surgical resection or definitive chemoradiation) **OR**
        ii. in patients with metastatic NSCLC

iii. **AND** PD-L1 expression (tumor proportion score [TPS] ≥1%) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations as determined by an FDA-approved test.

c. First-line treatment (in combination with pemetrexed and platinum chemotherapy) of metastatic non-squamous NSCLC in patients with **NO** EGFR or ALK genomic tumor aberrations.
d. First-line treatment (in combination with carboplatin and either paclitaxel or paclitaxel [protein bound]) of metastatic squamous NSCLC.
e. Treatment of resectable NSCLC (tumors ≥4 cm or node positive) in adults as neoadjuvant treatment (in combination with platinum-containing chemotherapy), and then continued as adjuvant monotherapy after surgery.
f. Monotherapy of metastatic NSCLC in patients with PD-L1 expression (TPS ≥1%)
    i. **AND** with disease progression on or following platinum-containing chemotherapy as determined by an FDA-approved test.
    ii. Patients with EGFR or ALK genomic tumor aberrations should have disease progression (on approved EGFR- or ALK-directed therapy) prior to receiving pembrolizumab.

4. Head and Neck Squamous Cell Cancer (HNSCC)

a. In combination with platinum and fluorouracil (FU), for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.
b. 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.
c. As a single agent, for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

5. Classical Hodgkin Lymphoma (cHL)

a. For the treatment of adult patients with relapsed or refractory cHL
b. For the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more prior lines of therapy.

6. Classical Hodgkin Lymphoma (cHL) and Adult Primary Mediastinal Large B-Cell Lymphoma

a. Adult patients ONLY: Additional Dosing Regimen of 400 mg Every 6 Weeks

7. Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

a. For the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy.
b. Limitations of Use: Keytruda is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

8. Urothelial Carcinoma

a. For the treatment (as a single agent) of patients with locally advanced or metastatic urothelial carcinoma who:
    i. Are not eligible for any platinum-containing chemotherapy, **OR**
    ii. Who have disease progression during or following platinum-containing chemotherapy **OR**
    iii. within 12 months of neoadjuvant **OR** adjuvant platinum-containing chemotherapy.
b. For the treatment (as a single agent) 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.
c. Use in combination with enfortumab vedotin for the treatment of locally advanced or metastatic urothelial cancer in adults.

9. Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient Cancer (dMMR)

a. For the treatment of adult and pediatric patients with unresectable or metastatic MSI-H **OR** dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.
b. Limitations of use: The safety and effectiveness of Keytruda in pediatric patients with MSI-H central nervous system cancers have not been established.

10. Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC)

a. For the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test.

11. Gastric cancer

a. First-line treatment (in combination with trastuzumab and fluoropyrimidine- and platinum-containing chemotherapy) of locally advanced unresectable or metastatic **HER2-positive** gastric or GEJ adenocarcinoma in adults whose tumors express PD-L1 (CPS ≥1), as determined by an FDA-approved test.

b. First-line treatment (in combination with fluoropyrimidine- and platinum-containing chemotherapy) of locally advanced unresectable or metastatic **HER2-negative** gastric or GEJ adenocarcinoma in adults.

12. **Esophageal Cancer**

a. For the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
    i. In combination with platinum- and fluoropyrimidine-based chemotherapy, **OR**

ii. 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.

11. Cervical Cancer

a. Treatment (in combination with chemoradiotherapy) of FIGO 2014 stage III to IVA cervical cancer.
b. 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.
c. 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.

12. Hepatocellular Carcinoma (HCC)

a. Treatment of HCC secondary to hepatitis B in patients who have received prior systemic therapy other than a PD-1/PD-L1–containing regimen.

13. Merkel Cell Carcinoma (MCC)

a. For the treatment of adult and pediatric patients with recurrent locally advanced or metastatic MCC.

14. Renal Cell Carcinoma (RCC)

a. For the first-line treatment of adult patients with advanced RCC in combination with **ONE** of the following agents:
    a. Axitinib **OR**
    b. lenvatinib
b. For the adjuvant treatment of patient with RCC at intermediate-high **OR** elevated risk of recurrence following nephrectomy, **OR** following nephrectomy **AND** resection of metastatic lesions.

15. Endometrial Carcinoma, Advanced

a. In combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H **OR** pMMR, who have disease progression following prior systemic therapy in any setting **AND** are not candidates for curative surgery.
b. 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.

16. Tumor Mutational Burden-High (TMB-H) Cancer

a. For the treatment of adult and pediatric patients with unresectable or metastatic TMB-H [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test.
    a. have progressed following prior treatment **AND**
    b. who have no satisfactory alternative treatment options.

b. Limitations of Use: the safety and effectiveness of Keytruda in pediatric patients with TMB-H central nervous system cancers have not been established.

17. Cutaneous Squamous Cell Carcinoma (cSCC)

a. For the treatment of patients with recurrent or metastatic cSCC or locally advanced cSCC that is not curable by surgery or radiation.

18. Triple-Negative Breast Cancer (TNBC)

a. For the treatment of patients with high-risk early stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as adjuvant monotherapy after surgery.
b. 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.

Renewal.

Patient must have ONE of the following:

1. Unresectable or metastatic melanoma
2. Stage IIB, IIC, or III melanoma following complete resection.
3. Metastatic non-small cell lung cancer (NSCLC)
4. Metastatic nonsquamous non-small cell lung cancer (NSCLC)
5. Stage III non-small cell lung cancer (NSCLC)
6. Metastatic squamous non-small cell lung cancer (NSCLC)
7. Recurrent or metastatic head and neck squamous cell carcinoma (HNSCC)
8. Relapsed or refractory classical Hodgkin lymphoma (cHL)
9. Refractory primary mediastinal large B-cell lymphoma (PMBCL)
10. Locally advanced or metastatic urothelial carcinoma
11. Non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS)
12. Unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors
    a. NOT for use in pediatric patients with MSI-H central nervous system cancers
13. Unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer
14. Locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma
    a. Used in combination with trastuzumab, fluoropyrimidine- and platinum- containing chemotherapy.
15. Locally advanced or metastatic esophageal or gastroesophageal junction carcinoma
16. Persistent, recurrent, or metastatic cervical cancer
17. Hepatocellular carcinoma (HCC)
18. Recurrent locally advanced or metastatic Merkel cell carcinoma (MCC)
19. Advanced renal cell carcinoma (RCC) AND ONE of the following:
    a. First line treatment
        i. Used in combination with Inlyta (axitinib) OR Lenvima (Lenvatinib)
        ii. Prescriber agrees to monitor for hepatotoxicity.

    b. Adjuvant treatment
20. Advanced endometrial carcinoma
    a. Used in combination with Lenvima (lenvatinib)
21. Unresectable or metastatic tumor mutational burden-high (TMB-H) solid tumors
    a. NOT for use in pediatric patients with TMB-H central nervous system cancers
22. Recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC
23. Triple negative breast cancer (TNBC) and ONE of the following:
    a. High-risk early stage TNBC used as single agent as adjuvant treatment.
    b. Locally recurrent unresectable or metastatic TNBC used in combination with chemotherapy.
24. Biliary tract cancer (BTC)

AND the following:

1. Prescriber agrees to discontinue treatment for any immune mediated adverse reaction (encephalitis, nephritis, rash, decreased renal function and endocrinopathies) or disease progression.

If the above criteria are met, Prior Authorization is to be approved for a 6-month duration.

When Policy Topic is not covered

Keytruda (pembrolizumab) is considered **not medically necessary** when the above criteria are not met and **investigational** for all other uses.

Centers for Medicare and Medicaid Services (CMS)

When reviewing for a Medicare beneficiary, guidance from National Coverage Determinations (NCD) and Local Coverage Determinations (LCD) supersede the Medical Policies of Blue KC. Blue KC Medical Policies are used in the absence of guidance from an NCD or LCD.

In general, Medicare covers outpatient (Part B) drugs that are furnished 'incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals.

NCDs
https://www.cms.gov/medicare-coverage-database/search-results.aspx?keyword=&keywordType=starts&areaId=s29&docType=NCD&contractOption=all

LCDs
https://www.cms.gov/medicare-coverage-database/search-results.aspx?keyword=&keywordType=starts&areaId=s29&docType=F,P&contractOption=all

Considerations

Keytruda (pembrolizumab) requires prior authorization through the Clinical Pharmacy Department.

This Blue Cross and Blue Shield of Kansas City policy statement was developed using available resources such as, but not limited to: Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, local medical policies of other health plans, Medicare (CMS), local providers.

Description of Procedure or Service

Keytruda (pembrolizumab) is a monoclonal antibody for the treatment of patients with many diverse types of cancer. Keytruda blocks a cellular pathway known as PD-1, human programmed death receptor-1. When PD-1 is activated, it causes the immune cells to die, therefore restricting the body's immune system from attacking the cancer cells. Blocking PD-1 allows the immune cells to stay alive and allows for targeting of cancer cells.

Clinically significant immune-mediated adverse reactions may occur with Keytruda therapy including pneumonitis, colitis, hepatitis, hypophysitis, nephritis, hyperthyroidism, hypothyroidism, skin adverse reaction, infusion-related reactions, and other immune-mediated adverse reactions. Based on the severity of the adverse reaction, Keytruda should be withheld or discontinued, and corticosteroids administered. Keytruda may cause fetal harm when administered to a pregnant woman. Safety and effectiveness of Keytruda have been established in pediatric patients.

Keytruda in combination with axitinib can cause hepatic toxicity with higher-than-expected frequencies of Grades 3 and 4 ALT and AST elevations compared to Keytruda alone.

Rationale

Prior authorization is required to ensure the safe, clinically appropriate and cost-effective use of Keytruda (pembrolizumab while maintaining optimal therapeutic outcomes.

Warnings and Precautions

• Adverse reactions (immune-mediated): PD-1/PD-L1 blockers (including pembrolizumab) remove immune response inhibition, thus potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Severe and fatal immune-mediated adverse reactions may occur in any organ system or tissue. Reactions generally occur during treatment (may occur at any time after pembrolizumab initiation); reactions may also occur after pembrolizumab discontinuation. Early identification and management of immune-mediated adverse reactions are necessary to ensure safe use of pembrolizumab. If

suspected immune-mediated reactions occur, initiate appropriate workup to exclude alternative causes (including infection). Medically manage immune-mediated adverse reactions promptly and refer for specialty consultation as appropriate.

• Infusion-related reactions: Infusion-related reactions (including severe and life-threatening cases) have occurred. Signs/symptoms of a reaction included rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

Billing Coding/Physician Documentation Information

J9271	Injection, pembrolizumab

Policy Implementation/Update Information

01/2021	New policy titled Keytruda (pembrolizumab) – Medicare Advantage Only
06/2022	Annual review – no changes made
06/2023	Added Warnings and Precautions
04/2024	Updated all indications
06/2024	Annual review – Updated clinical indications

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